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Content

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EDITORIAL MESSAGE

India possesses a prominent position in the global pharmaceuticals sector. The Indian pharma industry, which is expected to grow over 15 per cent per annum between 2015 and 2020, will outperform the global pharmaceutical industry, which is expected to grow at an annual rate of 5 per cent between the same periods. Indian companies received 55 Abbreviated New Drug Application (ANDA) approvals and 16 tentative approvals from the US Food and Drug Administration (USFDA) in Q1 of 2017. The implementation of the Goods and Services Tax (GST) is expected to be a game-changer for the Indian Pharmaceuticals industry. It is expected to result in an efficient supply chain management, which is expected to reduce its cost considerably.

In the era of knowledge explosion, we need to keep ourselves updated with respect to recent trends in the pharmaceutical industry in research of drug discovery, development, diagnosis and therapy. The Nirma University Journal of Pharmaceutical Sciences (NUJPS) is a small step towards contribution in terms of improvement of the scientific knowledge in the area of Pharmaceutical Sciences. The Journal focuses on original research work, review articles or case studies on a current topic in Pharmaceutical Sciences. We are happy to release its fourth issue.

In this issue, we have invited articles from eminent experts from different facets of pharmaceutical field, postgraduate and undergraduate students.

We are thankful to all the faculty members, HODs, our Director as well as our Director General Dr. Anup Singh and the Nirma University authorities, stakeholders, reviewers for all the support provided in rolling out this issue. We hope that our efforts will help the readers to widen the horizons.

We look forward to your constructive criticism and suggestions.

Happy hours are here again!!

Editorial Team, NUJPS

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SHORT COMMUNICATION

SKILL GAP ANALYSIS IN LIFE SCIENCES SECTOR

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Life Sciences Sector Skill Development Council (LSSSDC) is an autonomous and not for profit organization with financial support from National Skill Development Corporation (NSDC). Life Sciences Sector comprises of industries in the areas of Pharmaceutical, Bio-Pharmaceuticals, Medical Devices and Contract Research. Life Science Sector required highly skilled personnel as it is connected with research and development. This sector relates with development, delivery and evaluation of life care products, which needs collaboration skills of academia, industry and government. If these issues are not addressed effectively, it may hamper the number of products in the market. The key objective of the LSSSDC is to create a robust and vibrant eco-system for quality education and skill development in the Life Sciences Sector in the country. LSSSDC works as an apex body in Life Sciences Sector for Skill Development Initiative in India. Three important missions of LSSSDC are:

- To carry out a functional and occupational mapping and to develop a catalogue of Industry Occupations/Job Roles in Life Sciences Sector.
- To develop and set National Occupational Standards for different job and its roles in the sector
- To develop and put in place an Assessment & Certification mechanism for Accreditation of Training Institutes/Trainees and Trainers

SKILL GAP STUDY

LSSSDC carried out skill gap study in 2014. Findings of the Skill Gap Report will be useful to stake holders of Educational Institutions in Life Sciences Sector in India. Important findings are:

- The industry is expected to employ 2.15 million people by 2024, with the highest gap in the manufacturing segment.
- The sector is expected to see a new job creation of 1.31 million between 2015

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to 2024 with the highest job creation in the manufacturing sector.

- For junior and entry level positions, attributes such as technical proficiency in labs, manufacturing instruments, subject knowledge (basic and superior), high learning aptitude and thinking and questioning ability are the key skills needed.
- The research functions are seen to possess adequate Organic and Analytical Chemistry related skills, but face concerns in biology related skills which need to be addressed.
- The exposure of handling high end equipment and new technology is still a gap for research function job roles at entry level.
- Need is felt for skill and capability building in quality, intellectual property and regulatory aspects at all levels.
- For senior and middle level employees, inadequate industry experience, lack of appropriate communication and interpersonal skills, superior technical competence and research ability are key skill gaps.
- There is an enormous research in area of system biology and bioinformatics. However, it is observed that mathematical and computational skill required for the same is the major gap to the researchers.
- Translational medicine and clinical pharmacology skills which requires complex understanding to bridge the gap between bench and bedside is also lacking in researchers
- Drug metabolism and ADME, pharmacokinetics and pharmacodynamics and *in-vivo* sciences skill is also found as gap in top skills in 2008.

CONCLUSION

One of the major challenge that our nation faces is non -employability of large sections of the conventionally educated youths who possess little or no job skills. However, there is a huge need to identify the need of particular skills depending upon life sector and role of job. Training for all types of skills could not fill the gap in life sector. This also requires revolution in education. The diversified syllabus touching cross disciplinary areas with training can make researcher different. Re-moulding of curriculum as well as curriculum delivery based on the findings in skill gap report of LSSSDC shall help in minimizing the challenge in Life Sciences Sector. It is expected that if these skills are taken care at each facet for employee in Pharmaceutical Industry, it can change the output and lots of innovative products will in market. The activities and plan of action for skill enhancement by forecasting future need by academic and industry is the important tool to decrease the gap in life skill sector.

References:

1. lsssdc.in

2. www.msde.gov.in

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REVIEW ARTICLE

CHEWING GUM: A BOON FOR ORAL DRUG DELIVERY

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Abstract

Different types of formulations including; mouth wash, lozenges, gargles, mouth dissolving films and pellets, chewing gums, etc. are being used to combat bad breath. Chewing gums have been used as a means of cleansing teeth and for removing bad breath odor, since a very long time. The prevalent use of chewing gums by people of all age groups has prompted interest of formulations scientist towards manufacturing of chewing gums for different purposes. Chewing gums are preferred for delivering drugs for localized effect as medicated chewing gums. Herbal ingredients are known to have a very pleasant and persistent mouth feel, however their use in the form of chewing gums is least explored. In this review authors have tried to compile the basic concept of formulating chewing gum, its method of production, characterizing parameters, various applications in different areas, future scope.

Keywords: Mouth feel, formulation, chewing gums.

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1. Introduction

Chewing gums are the agents which offer an alternative as well as a novel drug delivery system (1). Chewing gum have an old and long history (2). The Greeks used mastic, a resin from the bark of mastic tree for cleaning their teeth and improving the smell of breath. The Mayan Indians obtained gum from the sapodilla tree, a member of the family Sapotaceae for the same purpose (3). Due to certain limitations and the shortage of the natural gum, this paved out the way for synthetic gum during the period of World War 2 (4). Then after at the end of world war i.e. in the year 1948 for the first time chewing gum was marketed and commercialized by the name "state of Maine pure spruce gum"(4).

The first medicated chewing gum (MCG) containing an analgesic, acetylsalicylic acid (aspirin) was marketed in the 1928 by the name "aspergum" (5). However, it was not accepted in public domain un till 1978. With the introduction of nicotine chewing gum in the 1980s, the chewing gum begins to be accepted for use (6). Another chewing gum dimenhydrinate was commercially available for the treatment of motion sickness.

For the prevention and treatment of various oral diseases, an alternate class of antimicrobials comprising of naturally occurring antimicrobial peptides have been developed in the form of MCG. The aim of formulating such MCG was to effectively delivery and maintain a sufficient anti-bacterial dose within the oral cavity. Chewing gums have potential for sustained delivery of active agent, since they reside in the oral cavity for a longer period of time as compared to lozenges, tooth paste etc. and hence are preferred for the treatment of diseases pertaining to oral cavity (7).

This increasing use of chewing gum led the committee for medicinal products for human use (CPMP) to define medicated chewing gum as "A solid dose preparation with a base consisting mainly of a gum that are intended to be chewed but not to be swallowed, providing a slow steady release of medicine contained" this is reflected in European pharmacopoeia and the guidelines for pharmaceutical dosage form. Chewing gum has travelled such a huge path from the Mayan Indians to the present day, mainly due to it is ease of administration, easy and a quick manufacturing process, quick onset of drug release along with ease of termination to drug release (4). Pros and cons of chewing gum are described in table 1. Major advantages of oral drug delivery:

- By passing the gastrointestinal tract and hepatic portal system so fewer side effects
- Provides rapid onset of action (direct absorption through oral mucosa) and the formulation can be removed if the therapy is to be terminated
- Higher patient compliance

Table 1: Pros and cons of chewing gum

Pros	Cons
• A rapid onset of action is obtained. • The rate of salivation increases which modifies pH and helps in the treatment of acidity of gastric mucosa. • The drug has high bioavailability. • The drug released is in soluble form, which is an advantage over tablet dosage form. • They are ready to use type of dosage form. • It has a high patient compliance as it's administration does not require water. • It provides a pleasant taste. • It rules out the problem of swallowing tablets and hence is hi ghly accepted by children and patients. • It has very less side effects. • It helps in prevention of dental caries. • It removes the condition of dry mouth (xerostomia) • It helps in relieving stress • The released drug has high bioavailability due to very less first pass metabolism. • Highly attractive from the marketing perspective due to the product's distinctiveness.	• Salivary dilution causes a decrease in concentration of drugs. • Involuntary swallowing from oral cavity of the saliva causes wastage of the drug. • Drug release differs from patient to patient as per the patients chewing habit. • The risk of over consumption is high as compared to chewable tablets, lozenges etc. • Diarrhea and flatulence are caused by sorbitol containing chewing gum. • Chewing gum is found to st ick to the enamel dentures and fillers. • Earache in children and jaw pain in adults is observed by prolonged use of chewing gum.

2. Composition of chewing gum (8, 9)

A piece of chewing gum consists of gum core composed of the gum base. The gum base consists of the elastomer, plasticizers, fillers, elastomer solvent, etc. The amount of powdered sugar used for the coating determines the brittleness of the chewing gum. Chewing gum consists of both water soluble and water in soluble portion. The water-insoluble phase consists of gum base (insoluble gum base resin), elastomers and emulsifiers. While, the water-soluble phase consists of fillers, antioxidants, softeners, sweeteners, food colorings, flavoring agents etc. In the case of medicated chewing gum an active pharmaceutical ingredients (API) is present in addition to the above-mentioned ingredients. Generally, the water content of chewing gum is very less and so there is no need of preservatives (10). The details of excipients with their proportional representation and purpose of addition are mentioned in table 2.

Table 2: Excipients used for formulating chewing gum (11).

Excipient	General range	Function	Example
Elastomers	15-45%	Controls the gummy texture and provides elasticity to the gum base.	**Natural:** Chicle gum, crown gum, nispero etc. **Synthetic:** Butadiene-styrene copolymer, polyisobutylene, isobutyleneisoprene copolymers
Elastomers solvent	45-70%	Provides softness to the elastomeric base.	**Natural**: Partially Hydrogenated rosin, pentaerythritol esters or glycerol ester of rosin, glycerol esters of demineralized rosin. **Synthetic:** Terpenes (D -limonene, α and β-pinene)

Plasticizers	---	Provides Proper consistency and desirable texture to the gum base.	Lanoline, glyceryl triacetate, glycerine, propylene glycol monostearate, vegetable oil and different waxes from natural and synthetic origin.
Bulking agent	Quantity sufficient	Used to enlarge the bulk consistency in case of low calorie gum and in highly potent chewing gum.	Guar gum hydrolysates, indigestible dextrin, polydextrose, insulin, oligofructose, and fructooligosaccharide.
Softening agent	0.5-15%	They enhance the mouth feel and chew ability of chewing gum	Glycerin, lecithin and fatty acids(oleic acid, palmitic acid, linoleic acid, stearic acid, succinic acid)
Sweetening agents	<50%	To obtain desired amount of sweetness.	Sugars(sucrose, dextrose, glucose) Sugar alcohols (xylitol, Mannitol, sorbitol), aspartame.
Flavoring agent	0.01-1%	Provides different aroma and enhances the texture acceptability.	Volatile essential oils from both natural and artificial source like clove oil, fennel oil etc.

Coloring agent	0.1%	Provides a soothing color to the chewing gum and when used in corelationship with flavoring agent it increases acceptability.	Titanium dioxide, extracts obtained from plant and animal origin and the coal tar dyes approved by FD & C.
Antioxidants	0.02%	Prevents microbial growth.	Propyl gallate, butylated hydroxyl toluene, and butylated hydroxyl anisole.
Filling agents or compression adjuvants	<50%	They are used as aid in compression process.	Magnesium stearate, magnesium aluminum silicate, calcium carbonate, tricalcium phosphate, bentonite and talc.

Various ingredients used for formulating a medicated chewing gum are described in detail below (12):

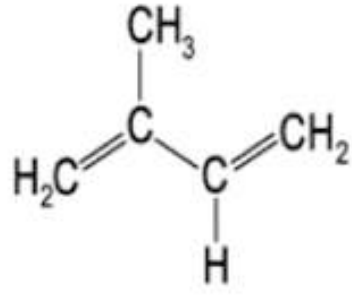
A) Gum base (1)

The gum base can be obtained from two types of sources - 1.) Natural and 2.) Synthetic

1) Natural

Gum base is obtained from trees are chicle like rubbery latexes or are the milky juices obtained by putting a cut on the plant part.

Natural gum chicle is commonly obtained from sapodilla tree *(Manilkara zapota L.)* belonging to the family sapotaceae. Chemically chicle is polyterpene which consists of thousands of C5H8 isoprene subunits (2-methyl-1,3-butadiene)



Isoprene unit

These gums as are obtained from natural origin are costly, has batch to batch variations etc. natural origin related disadvantages. Due to these reasons, it paved the way out for the use of synthetic materials as a gum base in chewing gum.

Example: Gum *(Pistachi mutica, Schiiuis molle),* Latex *(Asciepias eriocarpa, Euphorbia iorifera),* Resin *(E. agathisaustralls, Silpthum lacinatum),* Root bark *(Actinella siennis),* Ground bark *(B. lnuginosa),* Juice *(Tygodesmia juncea)* etc.

2) Synthetic:

Basic copolymers like butadiene-styrene, isobutylene-isoprene copolymer (butyl rubber), polyvinyl acetate, polyisobutylene, polyethylene etc. are used as synthetic gum base in chewing gum.

To reduce the adherence of the gum with teeth known as detackifier can be reduced by the usage of polyvinyl alcohol and polyvinyl acetate of different molecular mass it also aids in cutting down the chewing gum into pieces during chewing.

Gum base is the most important component of the chewing gum as it is present in highest amount (15-40%) so its amount determines the basic property of chewing gum such as texture, softness, hardness, elasticity, crumbliness, stickiness and mouth feel.

The gum base used are lipophilic in nature and as the most API are lipophilic in nature they adhere with the gum base by forming weak chemical bonding and so a slow release or incomplete release of API is observed.

To overcome this condition buffering or solubilizing agents can be added or coating/ encapsulation of API can be performed. While, the hydrophilic API gets released easily from the gum base and it needs to slow down its release by either encapsulating or by increasing the lipophilic content of the API.

B) Elastomers (2)

Elastomers provides elasticity to the gum base and also gives gummy texture to the chewing gum and are incorporated in to the chewing gum in the range of 15-45%.

Elastomeric solvents are added which aids in providing elasticity and softness to the chewing gum.

C) Plasticizers (13)

Plasticizers are added to the gum base to obtain proper consistency to the gum base and to give desirable texture to the chewing gum they are added to the chewing gum in varying concentration depending on the desired texture.

D) Bulking agent (3)

They are the agents used to increase the bulk of the chewing gum. The need to increase the bulk consistency of the chewing gum is needed in case of the MCG containing a very potent drug or for the drug which is to be given in very low

dose. It's also helpful for the diabetic patient by using a low-calorie gum.

E) Softening agents:

Softening agents increases the chew ability and enhances mouth feel by providing enormous softness during chewing.

F) Sweetening agents:

Sweetening agents are used to provide desired sweetness to the chewing gum

Sweetening agents can broadly be classified into two categories i.e. aqueous and bulk. While, the bulk sweeteners can be further classified into nutritive and non-nutritive bulk sweeteners.

The sweetening agents are selected for a formulation based on their safety, organoleptic qualities such as taste, odor and based on its stability in different pH conditions.

G) Flavoring agent:

Flavoring agent are used to provide the formulation a suitable flavor and also to increase the aroma of the chewing gum which enhances the acceptability of the product. They are generally added to musk out the taste of another undesired component used in the chewing gum. They are also used to overcome the bitter taste of the chewing gum. They are selected on the basis of another excipients and color used in the formulation.

Various flavors used for taste masking of different kind of drug are described in table 3.

Table 3: Approved flavoring agents of taste specific masking (10)

Taste of drugs	Flavors
Sweet	Honey, vanilla, bubble gum, Fruit and berry
Bitter	Wild cherry, raspberry, coffee, chocolate, mint, grapefruit, passion fruit, peach, orange, lemon, lime, anise
Acidic sour	Lemon, lime, orange, cherry, grapefruit, liquorice
Alkaline	Mint, chocolate, cream, vanilla
Metallic	Burgundy, berries, grape, marshmallow, Guyan
Salty	Butterscotch, maple, apricot, peach, melon, vanilla, wintergreen, mint

H) Coloring agent:

Coloring agent are used to provide soothing color to the chewing gum. They are generally used in accordance with the flavoring agents as both of them collectively increases the general acceptance of the chewing gum.

General source of coloring agent is various extract obtained from plant (chlorophyll-green, cur cumin-yellow) and animals (cochineal-red); various dyes obtained from the coal tar which are approved for its application in food and cosmetics by FD&C of various nations like brilliant blue, fast green, tartarazine, sunset yellow etc. Various synthetic opacifiers such as titanium dioxide and magnesium oxide are used to provide whiteness to the final product.

I) Anti-oxidants

Anti-oxidants are the agents used as a preservative which does not allow the oxidation of the chewing gum and thus has an anti-microbial property. It helps in increasing the general stability of the chewing gum and also helps in increasing the shelf life of the final product.

J) Filling agents:

They are also called as compression adjuvants. They aid in the compression process of chewing gum preparations as they deform very easily on compression, they also improve the flow property of the material and are used as a lubricant.

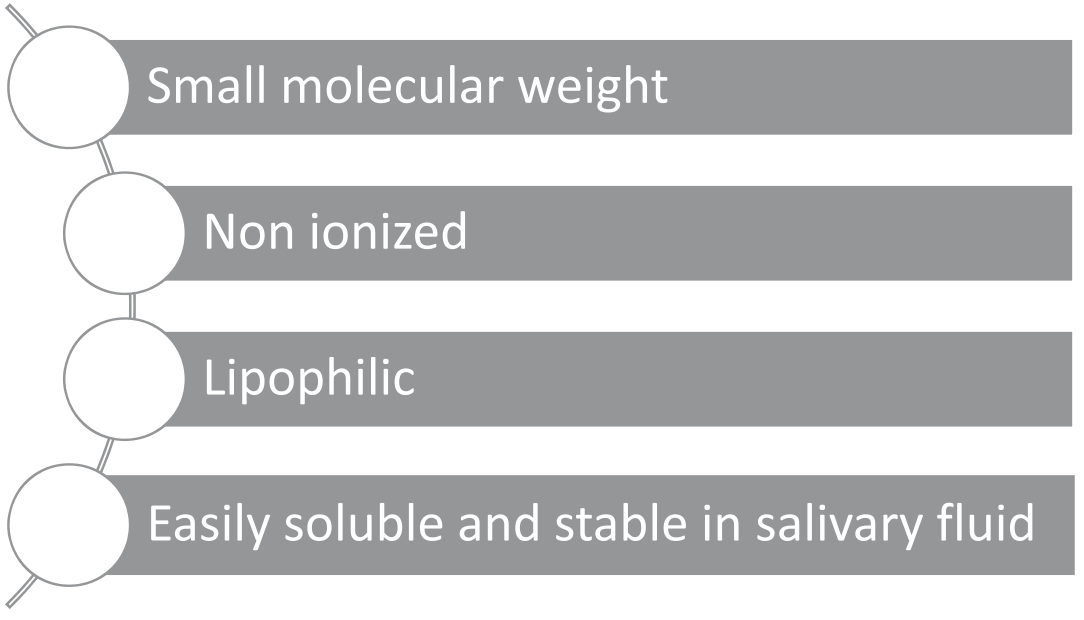


Figure 1. Desirable properties of drug (API)

3. METHOD OF PREPARATION OF MEDICATED CHEWING GUM (14)

1. Conventional method

This method is also called as fusion method. In this method, the gum base is softened or melted using a mixer. The active ingredient and other excipients are added to the melted gum base in a sequence. The resultant gum mixture is passed through a series of rollers that produce thin and wide ribbons. This are then allowed to cool and set properly. Finally, the gum is then cut into desired size and shape, followed by packing.

Thermolabile drugs cannot be incorporated as melting of gum base requires high temperature. Also, content uniformity cannot be achieved.

2. Freezing, Drying and Tableting Method

Freezing

The gum base is cooled such that it remains sufficiently brittle and would not adhere to the grinding apparatus during further processing. The temperature is usually set to 15° C or below.

Grinding

The previously refrigerated gum base is crushed to obtain fine fragments of the mixture. Additionally, anti caking agent like- silicon dioxide, are added to prevent adhesion during the process.

Tableting

The grinded gum base is mixed with active ingredient and other excipients such as, binder, lubricant, coating agent, sweetener, flavoring agent, etc., using a suitable blending machine. The blend is then mixed with anti-adherent talc or magnesium stearate. The final step involves compression with the aid of tablet compression machine.

3. Direct compression method:

The gum base is taken into a blender like v-shaped, cone shaped to this active agent is mixed directly for a specific period of time. Binder, sweetener, flavor and other excipients are added with continuous mixing.

The blend obtained is then mixed with talc or magnesium stearate in order to maintain the flow of the blend and prevent adhesion during compression. Lastly the blend is subjected to compression using tablet compression machine.

Factors affecting release of active ingredient

- Physicochemical properties of active ingredient: the saliva soluble ingredients will be able to give immediate release and quick onset of action. While poorly soluble ingredients will be slowly released.

- Formulation related factors: Amount and composition of the gum base effects the release of active ingredient.

- Contact time: The contact time of MCG has a direct impact on the local and systemic effect of the active ingredient incorporated.
- Inter patient variability: The chewing frequency, intensity and time affect the release of active ingredient from the MCG.

Table 4 : Factor affecting the release of API form MCG

Factors affecting the release of API from MCG	
1.)	Contact time
2.)	Chewing rate
3.)	Physical and chemical property of API
4.)	Physical and chemical property of API
5.)	Person to person variation
6.)	Formulation factors
7.)	Environmental factor
8.)	Rate and amount of saliva production
9.)	Manufacturing process
10.)	Pka value of the drug

4 CHARACTERIZATION OF MCG (11, 15)

1 Pre-compression parameters

1.1 Bulk density (16, 17)

The bulk density of the powder is the mass of the powder divided by the volume occupied by the powder. The bulk density is determined by allowing the dispersed powder to settle down under the influence of the gravity inside a specific container. Powders consisting of the high structural strength resist settling down and possesses low bulk density. While the one with low structural strength settles down easily and possesses high bulk density. Bulk density is defined by the following equation:

Bulk density = Mass/Volume

1.2 Tapped bulk density (18)

The tapped density of a specific powder can be obtained by tapping the container containing the dispersed powder sample.

The tapping is performed at a specific rate for a specific period of time from a definite height until the constant volume of the powder is obtained.

The powder possessing high cohesive force shows a high amount of reduction of volume on tapping. While the free-flowing powder does not show any significant amount of reduction on tapping.

Tapped density =
(Mass of tapped material) /
(Volume of tapped material

1.3 Carr's index (19)

Carr's index is also known as carr's compressibility index. It is used to study the compressibility of a powder.

$$C = 100 ((Vb-Vt)/Vb)$$

Where Vb is the volume of powder occupied when let to settle freely, Vt is the volume occupied by the same amount of powder after tapping.

Carr's index is frequently used to determine the flowability of the powder. The free-flowing powder has a very small difference between the Vb and Vt, giving the small amount of carr's index. While poor flowing powder has high carr's index.

1.4 Hausner's ratio (20)

Hausner's ratio is the ratio of the tapered bulk density to the aerated bulk density. It is helpful in the measurement of the cohesion property of the powder. A decrease in the hausner's ratio directly corresponds with the decrease in the cohesiveness of the powder and vice-versa.

$$H = \rho t/\rho b$$

Where, ρt is freely settled bulk density of material, ρb is tapped density of material

2.0 Sensory evaluation of MCG (14)

With the help of the panel of human volunteer's sensory evaluation can be performed. The volunteers can be guided to chew the chewing gum for specified period. A score card for the evaluation of can be made based on which the appropriateness felt by them on following parameters:

2.1 Chewability

2.2 Grittiness

2.3 Taste

2.4 Sweetener lasting time

3.0 Texture profile analysis

In order to determine the softness of the MCG, texture profiling can be done. This analysis gives a graph of load vs time, which gives estimate of the chewability.

4.0 In vitro drug release (9, 21, 22)

For the in vitro drug release study of MCG two different types of chewing apparatus has been proposed. (a) Unofficial single-module chewing apparatus and (b) official MCG chewing apparatus.

(a) Unofficial single-module chewing apparatus:

Weenergren designed the first dissolution studying apparatus which consisted of two horizontal pistons and a reservoir whose temperature can be controlled. A jaw with the flat lower surface is parallel to central part of the lower surface. A brim is angled upward at about 45° so that lower surface functions as a bowl preventing the gum to from sliding during mastication. On compression of piston the MCG gets compressed and makes a twisting association.

(b) Official MCG chewing apparatus:

The apparatus for MCG was adopted by the European pharmacopoeia in the year 2000. It consists of two horizontal the pistons known as teeth, a chewing chamber and a vertical piston known as the tongue. The tongue works alternatively with the teeth its function is to ensure that gum is positioned in correct place during the mastication process. The horizontal piston is rotated in opposite direction on its own axis which gives the maximum mastication.

The temperature of the chewing chamber is maintained at 37±0.5° Celsius. The chew rate, the volume of the medium, jaws distance, twisting angles etc. can be varied according to the requirements. The European pharmacopoeia recommends the usage of 40ml of chewing chamber consisting of 20ml of the buffers (pH around 6) and with a chew rate of around 60 strokes per minute.

5.0 Applications of MCG (15)

5.1 Smoking cessation

Due to masticatory effect of MCG containing nicotine in very mild quantities, it gives aids by giving a feeling of smoking sensation. This prevents the patient for actually undergoing the act of smoking. Thus, chewing the MCG can reduce smoking.

5.2 Bad smell

The ingredients used in MCG have a strong flavor and mouth feel. This helps to remove the bad smell occurring after eating some strongly flavored eatables like onion, garlic etc.

5.3 Dental caries

Pediatric and geriatrics age group people suffer from dental caries. It is difficult for doctors to treat them. Hence MCG serve the purpose. These age group people are given MCG containing drugs which cure dental

caries. The more they chew the chewing gum the more is the drug released in mouth cavity and thus provides relief from dental caries

5.4 Pain

MCG provides relief from the tooth and gum related pain.

5.5 Fungal infections

Fungal infections in mouth cavity are difficult to cure. Since the mouth cavity is full of moisture all through day and night. MCG aids in curing fungal infection by continuously releasing the loaded medicament within the mouth cavity. Thereby providing relief from fungal infections.

5.6 Treat xerostomia caused by drugs like opioids, antidepressants and sedatives.

5.7 Other indications like anxiety, motion sickness, allergy, cold and cough, acidity, diabetes etc.

6.0 Future trends

Since old age, chewing gums have been able to attract people of different age groups as a mouth freshener. The use of chewing gum as a drug delivery system is a new trend and as it has got several benefits over conventional drug delivery system like- it has got both local and systemic effect, it bypasses first pass metabolism effect, fewer chances of toxicity, high patient compliance etc. since new and new NDDS are being formulated to reduce the surgical remedy of the disease, MCG can be seen as a reliable drug delivery system. While, economically chewing gum has become a multi- million-dollar industry and about one and a half million tons of chewing gum is sold in a year. The U.S. food and drug administration has accepted chewing gum as non-carcinogenic as the sugar substitutes are not used up by the oral bacteria. Hence, the MCG has a bright future ahead.

References:

1. Imfeld T. Chewing gum—facts and fiction: a review of gum-chewing and oral health. Critical reviews in oral biology & medicine. 1999;10(3):405-19.

2. Shah KR, Mehta TA. Medicated chewing gum-A mobile oral drug delivery system. Int J Pharm Tech Res. 2014;6(1):35-48.

3. Surana AS. Chewing gum: A friendly oral mucosal drug delivery system. International Journal of Pharmaceutical Sciences Review and Research. 2010;4(2):68-71.

4. Rassing MR. Chewing gum as a drug delivery system. Advanced drug delivery reviews. 1994;13(1-2):89-121.

5. Woodford D, Lesko L. Relative bioavailability of aspirin gum. Journal of pharmaceutical sciences. 1981;70(12):1341-3.

6. Jacobsen J, Christrup LL, Jensen N-H. Medicated chewing gum: Pros and cons (Healthcare Technology Review). American journal of drug delivery. 2004;2(2):75-88.

7. Faraj JA, Dorati R, Schoubben A, Worthen D, Selmin F, Capan Y, et al. Development of a peptide-containing chewing gum as a sustained release antiplaque antimicrobial delivery system. Aaps Pharmscitech. 2007;8(1):E177-E85.

8. Peters D, Denick Jr J, Talwar AK. Chewing gum compositions containing magnesium trisilicate absorbates. Google Patents; 1987.

9. Siewert M, Dressman J, Brown CK, Shah VP, Aiache J-M, Aoyagi N, et al. FIP/AAPS guidelines to dissolution/in vitro release testing of novel/special dosage forms. AAPS PharmSciTech. 2003;4(1):43-52.

10. Chaudhary SA, Shahiwala AF. Medicated chewing gum–a potential drug delivery system. Expert opinion on drug delivery. 2010;7(7):871-85.

11. Nagaich U, Chaudhary V, Karki R, Yadav A, Sharma P. Formulation of medicated chewing gum of ondansetron hydrochloride and its pharmacokinetic evaluations. International journal of pharmaceutical Sciences and Research. 2010;1(2):32-9.

12. Aslani A, Rafiei S. Design, formulation and evaluation of nicotine chewing gum. Advanced biomedical research. 2012;1.

13. Gadhavi A, Patel B, Patel D, Patel C. Medicated Chewing Gum-A 21st Century Drug Delivery Sysytem. International Journal of Pharmaceutical Sciences and Research. 2011;2(8):1961.

14. Maggi L, Segale L, Conti S, Machiste EO, Salini A, Conte U. Preparation and evaluation of release characteristics of 3TabGum, a novel chewing device. European journal of pharmaceutical sciences. 2005;24(5):487-93.

15. Khatun S, Sutradhar KB. Medicated chewing gum: An unconventional drug delivery system. 2012.

16. Abdullah E, Geldart D. The use of bulk density measurements as flowability indicators. Powder technology. 1999;102(2):151-65.

17. Shah RB, Tawakkul MA, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. Aaps Pharmscitech. 2008;9(1):250-8.

18. Hausner HH. Powder characteristics and their effect on powder processing. Powder Technology. 1981;30(1):3-8.

19. Lee T, Hsu FB. A cross-performance relationship between Carr's index and dissolution rate constant: The study of acetaminophen batches. Drug

development and industrial pharmacy. 2007;33(11):1273-84.

20. Tan S, Newton J. Powder flowability as an indication of capsule filling performance. International Journal of Pharmaceutics. 1990;61(1-2):145-55.

21. Rider JN, Brunson EL, Chambliss WG, Cleary RW, Hikal AH, Rider PH, et al. Development and evaluation of a novel dissolution apparatus for medicated chewing gum products. Pharmaceutical research. 1992;9(2):255-9.

22. Kvist LC, Andersson S-B, Berglund J, Wennergren B, Fors SM. Equipment for drug release testing of medicated chewing gums. Journal of pharmaceutical and biomedical analysis. 2000;22(3):405-11.

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REVIEW ARTICLE

ADVANCES IN Tau PROTEIN INHIBITORS FOR ALZHEIMER'S DISEASE - A REVIEW

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Abstract

Alzheimer's disease was originally defined as presenile dementia which has no an antecedent cause, for example alcohol, stroke on brain or a trauma on brain. It is neurodegenerative disease which is chronic in nature which starts slowly and as time passes get worsen. Neurofibrillary tangles composed primarily of tau proteins aggregates which are hyperphosphorylated forms of the microtubules associated protiens. The main reason of aggregation is an imbalance in phosphates and kinase activities leading to an abnormal phosphorylation of tau and its further aggregation. A wide range of therapeutic approaches for this specific tau kinase inhibition or to enhance the phosphate activity, which will indeed promote the stability of microtubule and thus will in turn reduce the aggregation of tau proteins and their clearance is also enhance its clearance by small molecule drugs or by means of immunotherapy. Most of the drugs which are promising in their activities are still in preclinical trails and some of them are: Crenezumab (a monoclonal antibody which is passive); ACI-24 & -35 (targets aβ and p-tau actively as an immunotherapy), Anti- tau antibody and Morphomer tau (compound which is small for the treatment). Thus this therapy improves current situation of patient and blocks tau protein aggregation leading cause of AD.

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INTRODUCTION TO ALZHEIMER'S DISEASE:

Alzheimer's disease was originally defined as presenile dementia, but it now appears that the same pathology underlies the dementia irrespective of the age of onset. AD is alluded to dementia which happens with no reason, for example, stroke, cerebrum injury or liquor. It is perpetual neurodegenerative ailment that more often than not begins gradually and deteriorates after some time. It is the reason for 60% to 70% of instances of dementia. The most widely recognized side effect is loss of memory at little timeframe and it is seen in beginning period (here and now memory misfortune). As the sickness progresses, manifestations can incorporate issues with dialect, confusion (counting effectively getting lost), inclination swings, loss of inspiration, not overseeing self care, and behavioral issues. In spite of the fact that the speed of movement can shift, the normal future after determination is three to nine years. The sickness course is divided into four stages, with a progressive pattern of cognitive and functional impairment:

1) Pre- dementia
2) Early
3) Moderate
4) Advanced

STATISTICS: An expected 5.4 million Americans of the sum total of what ages have Alzheimer's illness in 2016. This number incorporates a 5.2 million individuals age 65 and more seasoned, and roughly 200,000 people under age 65 who have more youthful beginning Alzheimer's. 1in 9 individuals age 65 and more seasoned (11 %) has Alzheimer's sickness. Around 33% of individuals age 85 and more established (32%) have Alzheimer's malady. Eighty-one percent of individuals who have Alzheimer's ailment are age 75 or more established. . A larger number of ladies than men have Alzheimer's sickness and different dementias. Just about 66% of Americans with Alzheimer's are ladies. Of the 5.2 million individuals age 65 and more seasoned with Alzheimer's in the Unified States, 3.3 million are ladies and 1.9 million are men. In view of assessments, among individuals age 71 and more established, 16% of ladies have Alzheimer's sickness and different dementias contrasted and 11% of men.

PATHOPHYSIOLOGY OF ALZHEIMER'S:

There are mainly two pathways for the metabolism of amyloid precursor proteins (APP) i.e. physiological pathway and amyloidogenic pathway. In the physiological pathway APP in the presence of α-secretase enzyme and gets activated which in turn activates the function of growth factors. In the amyloidogenic pathway the APP in presence of β&ϒ-secretase enzyme converts it to two different forms Aβ-40 and Aβ-42 in alzheimer's the concentration of Aβ-42 is more thus on aggregation this both proteins they form oligomers and further converted to amyloid plaques which causes inflammation, mitochondrial damage and creates oxidative stress and thus causes

neuronal death. Alternatively the oligomers formed combines with kinase in turn activating tau to activated tau - pyrophospho proteins and reversible reaction via phosphatase which in turn forms neurofibrillary tangles and thus causes neuronal death.

PATHOPYSIOLOGY OF TAU PROTEINS ON AD AND INHIBITION OF TAU AGGREGATION:

As seen in the pathophysiology of the AD the formed oligomers can be stopped for further division by many different ways kinase inhibitors are used which stops the activation of the tau proteins. Then methylene blue is also used for the treatment and folic acid is also used for the treatment.

RECENT ADVANCES IN DRUGS USED IN ALZHEIMER'S DISEASE:

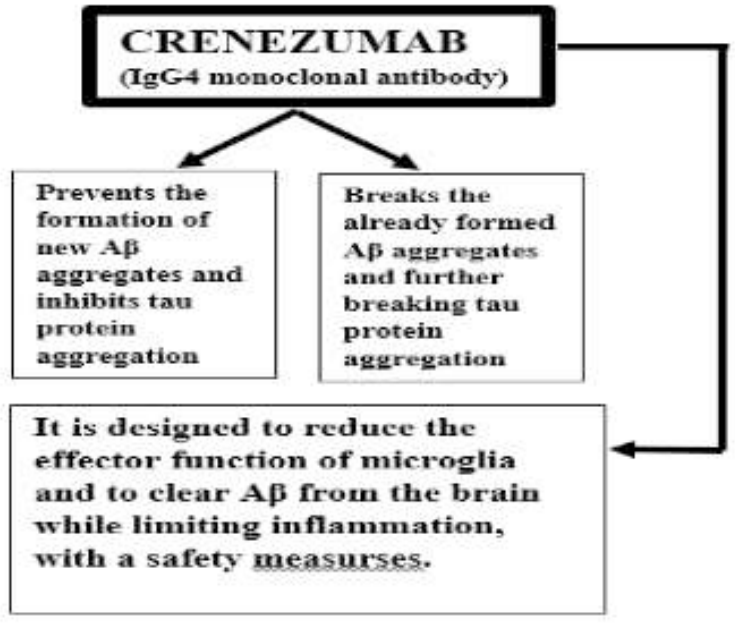
There are currently 5 inhibitors for the treatment of AD under research namely: crenezumab, ACI-24, ACI-35, antitau antibody and morphomer tau. All this drugs are under clinical trials and have shown promising result during the preclinical trials and are now under different phases of clinical trials.

CRENEZUMAB:

It is an aloof approach for immunotherapy in which treatment to patients is given with monoclonal antibodies that perceives Aβ peptides particularly. It perceives various types of accumulated Aβ, incorporating monomeric Aβ with low proclivity, oligomeric and fibrillar species and amyloid plaques with high partiality. This immune response mostly utilizes IgG4 as spine. It clears abundance Aβ while applying impact on microglia; it animates phagocytosis of amyloid and maintain a strategic distance from symptoms like vasogenic edema.

Clinical trials: Stage 1 trials were directed in two gatherings of individuals one in solid volunteers and other with Alzheimer's this were the security trails in which no indications of vasogenic edema or cerebral microhemorrhage, which permitted Stage 2 in which higher measurements were utilized to accomplish higher presentation to mind than was conceivable with past immunotherapy approaches. A Stage 2 trial a dosage of 15 mg/kg every long stretch of crenezumab subcutaneous infusions, it was directed in North America and Europe in 450 individuals with mellow to direct Advertisement. ABBY and a 91-understanding biomarker think about was called Blast and in spring 2014 it got finished. ABBY missed its essential endpoints of progress on ADAS-machine gear-piece and CDR-Cry. The investigation announced that treatment and fake treatment bunches isn't isolated on the essential endpoint of PET amyloid imaging, however reported a partition on the auxiliary endpoint of CSF Aβ. Crenezumab is likewise being tried in a counteractive action. In a five year contemplate which was begun in 2013, crenezumab was assessed as a major aspect of the Alzheimer Anticipation Activity and is first utilized as immunotherapy. At the season of enrolment the members in this

trial did not meet criteria for gentle subjective hindrance. This trial utilized a composite comprising of five separate intellectual tests for the essential result. A broad rundown of auxiliary results were likewise utilized, including security, time to movement to MCI, and also clinical results and liquid and imaging biomarkers. In Stage 2 trial 300 members were relied upon to be selected and it would keep running till 2020. In February 2015, a Stage 1b think about was begun in 72 individuals with three dosages of intravenous crenezumab and fake treatment were contrasted having mellow with direct Promotion. Dosages were not uncovered, but rather a course of 3-month of two imbuements month to month was trailed by an alternative of year open name dosing. In July 2015, crenezumab went into Stage 3, at first prodromal Promotion was examined. In January 2016, an investigation in 750 individuals' enrolment with MCI or prodromal Promotion with biomarker confirmation of Aβ pathology was begun. This trial utilizes change on the CDR-SB as essential result and a scope of intellectual and useful measures as auxiliary results. In this manner was called CREAD and it utilized 233 examination areas all around and is required to keep running until 2020. In 2016 consequences of the 72-quiet stage 1 trial, was reported. It asserted that both datasets anticipated a more grounded treatment advantage from the higher dosage of 60 mg/kg of crenezumab injected once every month for the CREAD Stage 3 contemplate, which was later on affirmed that previously mentioned measurement was assessed. On February 28, 2017, air conditioning Insusceptible reported that Genentech had chosen to begin a moment stage 3 trial of 750 members with prodromal to gentle Promotion, which is called CREAD2.



ACI-24: It is a liposomal restorative hostile to Abeta immunization fortifies a patient's invulnerable framework to deliver antibodies that particularly focus on the oligomeric and fibrillary Aβ proteins to forestall beta amyloid plaque collection and to upgrade plaque leeway. It is presently under stage 1 or 2B. Preclinical information demonstrates a noteworthy movement in plaque decrease and memory reclamation and has an absence of neighborhood aggravation and a method of activity free of fiery Lymphocytes. ACI-24 is as of now in a stage 1/2a clinical investigation in patients with gentle to direct Promotion.

ACI-35: It fortifies invulnerable framework to deliver antibodies against the misfolded and phosphorylated pathogenic types of Tau protein which makes neurofibrillary tangles one of the real signs of Alzheimer's ailment. It is at present under stage 1B clinical trials. In preclinical testing it gave counter acting agent reaction that was very particular to pathogenic Tau and brought about a decrease of both misfolded and phosphorylated Tau. ACI-35 is as of now in a clinical stage 1b ponder in patients with gentle to direct Alzheimer's illness.

ANTI-TAU ANTIBODY: The anti-Tau monoclonal antibody was authorized to Genentech in 2012 and contains monoclonal adapted antibodies which is particular for obsessive Tau. This medication is at present under stage 1 clinical trials.

MORPHOMER TAU: Hinders the conglomeration and seeding procedure of misfolded proteins and advance the disaggregation of effectively framed protein totals. It is still under preclinical trials. Preclinical examinations propose lessening of neurotic Tau totals prompting memory change.

CONCLUSION:

Alzheimer’s disease poses a lot of burden on the society. Current treatments are not able to produce complete cure of the disease. Crenezumab can possibly be a standout amongst the most encouraging treatments for this major worldwide ailment. ACI-24 is used for passive immunotherapy for Alzheimer’s disease and specifically acting passively on Aβ aggregates. ACI-35 is an active immunotherapy for Alzheimer’s disease targeting p-tau. Morphomer tau is a small molecule for AD treatment. Anti-tau antibody is a specific antibody for ptau. With better understanding of novel targets, drugs can be designed in future to improve the condition and benefit the society.

REFERENCES:

i) Wischik C, Storey J.; Alzheimer’s Disease– Amyloid, Tau and beyond: Tau Aggregation Inhibitor therapy for Alzheimer’s Disease; Biochem. Pharmacol. 2016; 88 (4): 529-539.

ii) Bateman R., Berry S.; The DIAN-TU Next Generation Alzheimer's prevention trial: Adaptive design and disease progression model;

Alzheimer's and Dementia. J Alzh Asso. 2017; 13 (1): 8.

iii) Statistical data from: https://www.alz.org/documents_custom/2016-facts-and-figures.pdf.

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REVIEW ARTICLE

EMA EXPECTATION WITH THE REVISED GUIDELINE OF RISK MANAGEMENT PLAN [GVP MODULE V]

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Abstract

The European Medicines Agency (EMA) has revised the guideline of Risk Management Systems (Revision 02). This article provides the expectation of EMA with recently published revised guideline of Risk Management Systems (Revision 02).

Keywords: European Medicines Agency, Risk Management Plan

Introduction

The European Medicines Agency has revised the Good Pharmacovigilance Practices (GVP) Module V on Risk Management Systems. The revised module (Revision 02) is effective from March 31, 2017. These revisions to the GVP Module V are intended to provide a more concise and clear description of risk management and how safety risks evolve through a product's lifecycle based on the evidence from a variety of sources. The guidance is updated in parallel to an amended Risk Management Plan (RMP) template for initial marketing authorization application.

Major changes in revision 02 of RMP guideline

- Clarification of what RMPs should focus on in relation to an important identified or important potential risk and missing information
- Removal of duplication of information within GVP Module V

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- Guidance on the expected changes in the RMP during the life cycle of the product
- Updated requirements for different types of initial marketing authorisation applications, with the aim to create risk-proportionate, fit for purpose RMPs
- An amended RMP template for initial marketing authorisation application

The comparison between the initial guideline (version 01) and revised guideline of risk management systems (revision 02) [1-3]

Section of the RMP	Revised Guideline of RMP (Version 02)
Part II Module SVII	The significant change in the revised guideline is the presentation of Module SVII which differs significantly from the initial guideline, in keeping with the ongoing theme of focussing on the RMP as dynamic document and a risk-proportionate RMP. The significant changes are • Both important and unimportant risks are to be discussed with a justification as to why risks have been classified as not important • For each important identified risk and potential risk, an evaluation of the impact on the risk-benefit of the product • Missing information data are now also to be presented in this module
Part III Pharmacovigilance Plan	The revised guideline conveys that routine PV activities which go beyond adverse reaction reporting and signal detection should be described.
Part IV Post authorisation efficacy studies	The scope of this module is more restricted than the initial guideline. It conveys that this should only include a list of post-authorisation efficacy studies (PAES) imposed as conditions to the marketing authorisation or when included as specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances. If no such studies are required, RMP Part IV may be left empty.
Part V Risk minimisation measures	The revised guideline conveys that over time consideration should be given as to whether additional risk minimisation measures could be removed.
Annexes	The initial guideline of RMP contains twelve annexes, while the revised RMP contains only eight annexes.

Transitional arrangements for RMP version 02

According to EMA, RMPs submitted for initial marketing authorization applications and D121 responses applying GVP Module V Rev 1 will be accepted for a further 6 months, and all other RMP submissions (including D91 responses for an initial application under accelerated assessment) will be accepted for one further year until 31 March 2018. Thus, all RMPs submitted after 31 March 2018 will be required to be submitted in accordance with revised guideline of RMP and comply with the Revision 02 format.

Conclusion

The revised guideline of the RMP and the RMP template provide substantive changes for RMPs and provide a welcome risk proportionate approach. The documents have provided clarification on previous grey areas and allow clearly for a change to the risk profile over time with the opportunity to remove or modify risks as appropriate. As a result it is likely that a more scientifically valuable RMP will be created which is better adapted to considering the use of the product in the real world setting over time.

References

[1] Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 1) Dated 15 April 2014 Available at https://www.scribd.com/document/336440833/Guideline-on-good-pharmacovigilance-practices-GVP-Module-V-Risk-management-systems-Rev-1-pdf

[2] Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) Dated 28 March 2017 Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf

[3] NEW! EMA Guidance on RMPs in the EU Dated 03 April 2017 Available at http://www.ubc.com/blog/new-ema-guidance-rmps-eu.

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REVIEW ARTICLE

CORRELATION OF MAJOR FACTORS AND CO-MORBIDITIES TO ADHD (ATTENTION DEFICIT HYPERACTIVITY DISORDER): A SYSTEMATIC REVIEW

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Abstract

ADHD (Attention Deficit Hyperactivity Disorder) a neurobehavioral disorder mainly occurs in pediatric age group. It is more prevalent in boys than girls. It is characterized by three common symptoms Inattention, Hyperactivity, and Impulsivity. The impairment of norepinephrine and dopamine neurotransmitter systems is the main cause of ADHD. There are many parameters which trigger this disease. Socio-economic factors, genetic variation, air pollution, or any co-morbid condition like mental retardation, epilepsy, Autistic Spectrum Disorder (ASD) like factors can trigger this disease. Evidences suggested that the age group children between 9 to 11 years are more prone to incidence and/or prevalence of disease. Temperament of the individuals can also leads to ADHD in some children. Various clinical and preclinical studies confirms that the brain is the most vulnerable part of the body for most of the pollutant. Sustained exposure to the vehicular pollution can affect ADHD. There is also some association between the 7-repeat allele of the dopamine D4 receptor gene (DRD4) and ADHD. The parental unipolar or bipolar affective disorder can also lead to childhood ADHD. The cytogenetic analysis shows various types of chromosomal aberrations observed in the ADHD patients. These aberrations include chromosome breaks, chromosome dicentric, and ring chromosome etc. so for effective treatment, it is necessary to prevent as well as to identify the correlation between ADHD and factors which triggered it.

Keywords: ADHD, Correlation, Co-morbidities, Factors, Attention Deficit Hyperactivity Disorder,

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Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder more prevalent in six to thirteen years of age in children [1]. Major three common symptoms of ADHD are inattentiveness, hyperactivity and impulsiveness. Inattention means lake of responsiveness towards stimuli, blunted errors in daily tasks, struggle in focus, being self-absorbed, and forgetfulness. Hyperactivity include violent behaviour, over excitation, altered gate with uncontrolled imagination and impulsivity includes disturbing teachers, sidetracking by calling out, struggling turn writing. Symptoms of ADHD occurs in childhood but also sometimes continue to adolescence [2]. According to symptoms three types of ADHDs are present inattentive, hyperactive-impulsive, and combined type as per the Diagnostic and Statistical Manual of Mental Disorder (DSM IV) from APA (American Psychiatric Association).

Current review enlightens several factors which are correlated to incidence or prevalence of the ADHD. It is essential to find out basic cause which are more prone for occurrence of the disease. It shows significant difference of the ADHD and non ADHD children with various parameters. So it is considerable that some of these factors are trigger factors for the disease. As a result, the child victim of ADHD can suffer from substantial mental illness, for instance difficulty to learn in institution and educational challenges [3], bothersome interactive affiliations with members within domestic environment, peers, and truncated self-confidence [4].

ADHD and Temper: Nature of child

Exhibition of regular behavioural pattern and perception toward the surrounding is called as Temperament. It comprehends the emotional, motivational, and responsiveness inside nature and works as a mirror in which a child views and communicate with his/her surroundings. Temperament is biologically compelled and obviously associated with inheritable factors which remains steady throughout time and circumstances. Temperament of the child is most crucial contrivance to diagnose ADHD. Two admiring perceptions are mostly applicable for temperament of child during reconnoitering the resemblances as well as variances of the theory with ADHD. Four most appropriate magnitudes to analyze temperament in school going children are; Negative reactivity (the strength and rate at which the child articulates destructive marks), perseverance during allotted task (period of attention), activity (motor conduct), and approach/withdrawal (primary reaction to novel settings) [5]. Previously conducted study reports the existence of 14% populace of children from 883 participants who were having temperament with “high maintenance” profile which include children having hyperactivity, negative reactivity and diminished task tenacity. Rothbart and her colleagues emphasized the association of alteration in provocation and distress with excitement, accomplishment of task, and contemplation [6] where they documented

that attention has both self-regulated and prompted characteristics. The buildup of attentional converging is associated to ability of child to endure attention during the course of drawn-out time. As the child grow ups he cultivates the aptitude for self-regulation [6]. If he can't do so that will spoil the career of the child. Child temperament is changed according to the hormone levels in some children but in other cases it is important that neurobehavioral impairment, traumatic condition or any head injury plays a role in child temperament despair. Child temperament is most important to determine for the assessment of mental condition of the child. A Previous study tells that combined subtype ADHD was allied with declined scoring during orientation of task and greater scores upon regular activity [7].

In previous study the pragmatic association of ADHD and temperament was analyzed amongst 70 male children with ADHD (n=35) as well as normal children (n=35) lied within age range between 5-8 years and rated by teachers and parents [8]. McIntosh and Cole-Love clinched that ADHD diagnosed children were having altered temperament and exhibiting hyperactivity, distractibility, and reduced persistence while that was opposite for normal children. Temperament of 8-10 years old 200 children both males and females were evaluated by Bussing et al. and positive responses were found upon Diagnostic Interview Schedule for Children (DISC) for the children with ADHD-combined subtype based on reports obtained by parents [6]. Children found with combined ADHD subtype obtained considerably greater ratings on the activity level-general dimension and apparently lesser score for coordination of task based paradigms when compared with non-ADHD children. Longitudinal study carried out upon 451 children by Lemery, Essex, and Smider exhibited commonality between magnitudes of behaviour of child upon Questionnaire of temperament, Preschool Behavior Questionnaire as well as the symptoms of ADHD on the MacArthur Health and Behavior Questionnaire [9]. To evaluate ADHD, the investigators utilized the multiple behavior problem related to attention deficit based on inattention and impulsivity subscales. When experimental and theoretical baffled queries were nullified, modest links persisted between the temperament dimensions of activity level, attentional centering, inhibitory control and ADHD symptoms of inattention and impulsivity.

Cytogenetic analysis

Several studies has been carried out to compare normal with ADHD children to monitor IQ (Intelligence Quest). Preceding reports upon ADHD children over and over again reveal declined IQ processes when compared with control children. Additionally more findings suggested negative relationship of hyperactivity with accomplishments and IQ level. It is the matter of quest that whether the deficient IQ based performance has any direct relation with ADHD. Role of genes in ADHD pathology has been accounted. Mutation in exon 3 on DRD4 gene positioned at chromosome 11 of human is

principally accountable for ADHD disorder [10].

Globally 3- 6% population under18 year age reveal ADHD symptoms. Both local and geographical variations are related with global genetic alteration and prevalence of disease. It is very significant to consider the role of insensitively and overactive-impulsivity indicators among conserved sex ratio and the cytogenetic aspects in association with chromosomal nature. In reported studies ADHD individuals showed abrupt informal alteration in chromosomal arrangement which include ring chromosomes, dicentric chromosomes and nicks in chromosomes. Available reports has by now advocated the general ADHD rate is as low as 2% and as high as 14% among school going children. In respects of this some reports denotes the nature and prevalence ADHD in the children less than 20 years because of high chromosomal aberrations rate. The probable gender variances and several biochemical i.e. hormonal alterations are expected to be the reason by which the males are more vulnerable to many developmental and neuro-cognitive incapacities. Neuroimaging reports have confirmed that girls are 20% less prone to develop ADHD [11]. Additionally, smaller amount of structural irregularities have been stated in the female brain with ADHD when compared with male with ADHD.

7-Repeat Allele of the Dopamine D Receptor Gene and ADHD

All available studies report the association between ADHD and 7-Repeat Allele of the Dopamine D Receptor gene. Even though availability of several case studies the theory explains DRD4 gene alteration establishes more important correlation with ADHD. Remarkably, in spite of the important meta-analysis reports, the outcomes of merely 2 from 14 family related studies were observed to be important. Additional contemplations advocate role of DRD4 in ADHD pathology. Dopamine and noradrenalin work as DRD4 agonists and their association with ADHD pathophysiology has been identified through both preclinical and clinical studies. Though several genes are associated with psychiatric abnormalities and works in harmonized manner, individual genes exert very little influence upon such illnesses. Even if the study to identify association of correct gene in such pathology is replicated there are very less probability to detect involvement of similar gene. To conduct replications to confirm role of previously detected gene there must be large samples to avoid uncertainties further meta-analytical statistics can resolve conflicting outcomes [8]. This technique helps to inspect whether the collective evidence through all existing knowledge delivers confirmation of statistically significant results in obtained informations. Therefore, to study the supposed connotation between DRD4 7-repeat allele and ADHD, meta-analysis of all existing family-based association and case-control studies are reported. Additional studies are necessary to explain what variant of DRD4 (or some nearby gene) is accountable for this association.

ADHD and Pollution

Exhaustion from transport services is related to respiratory and cardiac disorders in children however only some laboratory studies reveled its neurodegenerative outcome and associated cerebral anomalies in developing Asian countries like India. Human trials have proved that pollution leads to cerebral injury and loss of olfactory activity. The toys, the children play with are enriched with phthalates. Phthalates are industrial chemical added by manufacturers in the toys of children and devices for medical purpose to make them flexible and soft accompanied with some cosmetics to develop aesthetic smell [12].If the conceiving women inhales such toxic pollutant the upcoming child may suffer from attention insufficiency. Another pollutant is poly acrylic hydrocarbons (PAH) produced after burning of woods, fossils and garbage, found to be moderately fetal for health. Moreover upraised use of motor rides have abundantly elevated environmental carbon dioxide, carbon monoxide and PAH in environment. Recent study carried out by Mortamais et al., 2017 revealed role of PAH in ADHD. Brain imaging study of 242 young students with age group 8-12 years were carried out and it was found that PAH is linked with subclinical alteration in the caudate nucleus and modifies cognitive-behaviour process [13].

Food and Mood

Several findings have revealed that food governs mood of people through alteration in neuro-hormonal make up and energy requirements. Well-adjusted nutritional diet plan normalizes the mental and physical wellbeing of individuals. Remarkable deviations in youngster's life style led to extreme variations in their routine food consumption nature. A transference from deep-rooted foods to processed, precooked and instant foods is observed in every place of the world and Indian population imitate similar culture blindly. The processed food are prepared in western country as per their need. Indian ancient culture does not allow to do so in Ayurveda. It states that food which is safe to eat is contacted with sunlight at least once. Various aforementioned and current evaluations revealed an emotional and cognitive nature of person is affected the quality and nutritional values of food that the individual consumed. Certain diets can endure good mood while several diets boost debauched tempers or may create minor depression. Mediterranean diet is considered as the most balanced and the healthy eating assortment which are sufficiently enriched with fruits, vegetables, nuts, legumes, fish, cereals, and low fat dairy products and all of them carries important nutrient values. Healthy food creates the vigorous physique and healthy mental wellbeing. Antioxidant enriched fruits i.e. Indian gooseberry, Guava, Grapes, Pomegranate, and several fruits enriched with Vitamin-C prevent hyperactive as well as depressive behaviour by eradicating free radicals formation body and establish regular cellular activity. Children like junk foods which are rich cause of free radicals formation within body. Investigators identified that the people who were

deprived with folic acid were 67 % more prone to undergo depression than those enriched with it. Foods i.e. see foods, whole grain, nuts, legumes and beans are enriched with selenium which retard mild and moderate depression condition. An earlier data, published in the Journal of Trace Elements in Experimental Medicine, 1998; stated that individuals do not selenium rich diet are least are more confused, unsure and anxious than those who are taking it. Flax seeds and walnuts are enriched with omega-3 fatty acids, antioxidants and essential fatty acids which support to fight against depression, normalize mood, retard hyperactive behaviour and promote mental health [14]. Reports published in the British Journal of Nutrition denoted that consumption of food enriched with moderate amount of omega-3 fatty acids supports in execution of better cognitive and motor task as well as development of neuro-behavioural skills. Beverages and foods encompassing sugar and refined flour elevate blood sugar level which is followed by headache and moody crash. Several studies have revealed that ingestion of food consisting of excessive sugar, artificial color, preservatives and saturated fat exacerbate the typical ADHD symptoms in children. Cookies, puffs, dough nut, pastry, and numerous additional bakery foods comprising of Trans fatty acids originates inflammatory alterations in the body which may trigger sluggishness and depression [15].

If the condition is not handled seriously at later stage the ADHD child would be more prone to get low self-confidence, deprived social interaction and conflicting nature with the parents. So, during treatment of the ADHD children despite considering medical, scholastic and psychosocial interventions, dietary interventions must be considered. Awareness regarding ADHD symptom and diet can help caretakers and parents of the ADHD children to cope up with symptoms of it. An interdisciplinary assertiveness is essential which can be achieved by involvement of health departments, dietary interventions and investigators of scholastic foundations to regulate and manage this illness in an operational way.

ADHD and Ethnicity

Cultural environment surrounding child affects in several ways to the various aspects of central to mental health i.e. personality, language, conduct, emotion, attachment, attention, motivation, traumatic experiences, behavioral expectations and tolerance. Temperament of child is also exaggerated by the marital status of parents. There is diversified culture existed in world's different countries. It is important to find the composite relation between environmental and cultural dynamics to identify the ADHD phenomenon. Attachment and psychodynamic factors have not yet got as much attention that much they should be even though they are more culprit factors for development of ADHD. A child encountered traumatic illness may reveal series of signs identical to ADHD include; anxiety disorders and conduct disorders. Persistent traumatic state for instance negligence and exploitation of child or

failure to gain sheltered affection initially, may lead to form prolonged hyper provocative state in a child which modifies the neuroendocrine actions of cerebral milieu along with emotional, cognitive, and behavioral alterations. Child abuse is mainly succeeded by the cultural environment. The above discussed socioeconomic status of an individual is also the root cause of the economic status of the country. Cultural devotion and responsibility can also affect this disease. Hackett and Hackett addressed more strict expectations of Gujarati-speaking parents toward child behavior and there least tolerance with littler behavioural hitches [16]. Certainly, elevated parenteral expectations lead to exhibit fewer behavioural difficulties in children. Hence, the alterations in the ADHD rate across cultures or time is due to the variances in communal lenience [17].

ADHD and Major Mental Co-Morbidities

Among all ADHD children, 70% all reported for presence of co-morbid conditions like: autistic spectrum disorder (12.2%), mental impedance (28%) or epilepsy ((29.3%) [7]. ADHD children are with at higher risk to conduct substance abuse and mood associated symptoms [18].

ADHD and epilepsy

Population studies support the common occurrence of ADHD and epilepsy co-morbidity. A Review of literature between 1990−2014 reported 20−40% ADHD children to be epileptic [18]. ADHD and Epilepsy were documented to occur together higher than the expected rates and found to be the common co-morbid illness in infantile ages [20]. Predominance of ADHD in the childhood epileptic victims is 12 to 17%. Most of the concerned factor involved in such circumstances involve genetic susceptibility, dysregulation of noradrenergic system, seizures, subclinical epileptiform discharges, effects of antiepileptic drugs and socio-psychological issues [21].

ADHD is much predominant in early phase of epilepsy patient than normal one [22]. The presence of co-morbidity is identified by interview of parent, medical history, developmental history, family history, and evaluation of neurological symptoms. Boys are reported to be 3 times more susceptible for combined or hyperactive/impulsive ADHD when compared with girls.

ADHD and Mental Retardation

A child with insignificant psychological and intellectual impedance may not be diagnosed as the ADHD until their school years, when parents manifest the indications or cognitive disability, then after resuscitate to the child consultant for mental assessment. In most cases the physician can't consider this as the ADHD and assume that this is due to mental retardation and rarely prescribe the psychostimulants and ADHD remains uneradicated. A study published by Das et al. 1989 reported 33% of high school students both junior and senior were suffered with minor mental hindrance

exhibited ADHD characteristics [23]. Studies upon population suggested that mental retardation is 5-10 times more common in ADHD than in child lacking ADHD [24].

ADHD and Autistic Spectrum Disorders (ASDs)

ASDs are defined by abnormalities in social interaction, communication, and stereotyped or repetitive behaviour [25]. In a recent studies symptoms of ADHD like Inattention and Hyperactivity, are found common in individual diagnosed with ASDs. Current findings report involvement of >50% population from 487 youngsters and juveniles with modest to extreme ASD [4]. As a whole, it is projected that ADHD can arise in 14−80% patients who suffer with ASDs. Even though not being the prominent symptom, ADHD manifestations can be more devastating for the patients in cooperation with both the syndromes [26].

It is extremely difficult to correlate amongst ADHD along with mental retardation, childhood epilepsy as well as autistic spectrum disorders (ASD). Abundant features influence distinction in judgment of dominance and misty associations between these disorders. These relationships are going to be challenging for the researchers to enlighten.

Conclusion

From the above review it can be concluded that there are many physical, chemical, neurological, cultural, genetical, biological, factors those are in less or more actively can act as etiological factors for the ADHD. These factors are used to understand the disease progression or prevalence in the conditional aspect. The goal of the preventive health care can be fulfilled by this kind of review studies which are helpful in identifying the etiological factors for this disease and open the ways for further going research for researcher. Cultural impact also explains that the measures should be taken with the aim of to decrease the rapid percentage increase in the prevalence of ADHD globally.

References

[1] Onnink AMH, Zwiers MP, Hoogman M, Mostert JC, Kan CC, Buitelaar J, et al. Brain alterations in adult ADHD: effects of gender, treatment and comorbid depression. European Neuropsychopharmacology. 2014; 24(3):397–409.

[2] Biederman J, Petty CR, Clarke A, Lomedico A, Faraone SV. Predictors of persistent ADHD: an 11-year follow-up study. Journal of Psychiatric Research. 2011 feb;45(2):150–5.

[3] Zentall SSs. Research on the educational implications of attention deficit hyperactivity disorder. Exceptional Children. 1993; 60:143–15

[4] Soriano-Ferrer M, Félix-Mateo V, Begeny JC. Executive function domains among children with ADHD: do they differ between parents and teachers ratings? Procedia - Social and Behavioral Sciences. 2014; 132:80–6.

[5] Bussing, R., Gary, F. A., & Mason, D. M. Child temperament, adhd, and caregiver strain: exploring relationships in an epidemiological sample. Journal of the American Academy of Child & Adolescent Psychiatry. 2003; 42 (2), 184 – 192.

[6] Bussing R, Gary FA, Mason DM, Leon CE, Sinha K, Garvan CW. Child temperament, ADHD, and caregiver strain: exploring relationships in an epidemiological sample. Journal of the American Academy of Child & Adolescent Psychiatry. 2003; 42(2):184–92.

[7] Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch Gen Psychiatry. 1996; 53(7):607–16.

[8] Park S, Cho S-C, Hong Y-C, Oh S-Y, Kim J-W, Shin M-S, et al. Association between dietary behaviors and attention-deficit/hyperactivity disorder and learning disabilities in school-aged children. Psychiatry Research. 2012; 198(3):468–76.

[9] Gillis JJ, Gilger JW, Pennington BF, Defries JC. Attention deficit disorder in reading-disabled twins: evidence for a genetic etiology. Journal of Abnormal Child Psychology. 1992 ;20(3):303–15.

[10] Timimi S, Taylor E. ADHD is best understood as a cultural construct. The British Journal of Psychiatry. 20041;184(1):8–9.

[11] Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch Gen Psychiatry. 1996; 53(7):607–16.

[12] Polańska K, Jurewicz J, Hanke W. Exposure to environmental and lifestyle factors and attention-deficit / hyperactivity disorder in children — a review of epidemiological studies. International Journal Of Occupational Medicine And Environmental Health. 2012; 25(4):330–55.

[13] Mortamais M, Pujol J, van Drooge B, et al. Effect of exposure to polycyclic aromatic hydrocarbons on basal ganglia and attention-deficit hyperactivity disorder symptoms in primary school children. Environ Int. 2017;:12-19. doi:10.1016/ j.envint.2017.04.011.

[14] Omar A. N. Prevalence of attention deficient/hyperactivity disorder comorbidities in children of South

Jordan, European Scientific Journal, 2013, .9 (200); 236-38.

[15] Lerner Rm, Palermo M, Spiro III A, Nesselroade Jr. Assessing the dimensions of temperamental individuality across the life span: the dimensions of temperament survey (dots). Child development. 1982; 149–59.

[16] Mcclowry SG, Snow Dl, Tamis-Lemonda CS. An evaluation of the effects of insights on the behavior of inner city primary school children. The Journal of Primary Prevention. 2005; 26(6):567–84.

[17] Timimi S, Taylor E. ADHD is best understood as a cultural construct. The British Journal of Psychiatry. 2004 1; 184 (1):8–9.

[18] Calderon-Garcuduenas L, Maronpot RR, Tores Jardon R, Henriques Roldan C, Schoonhoven R, Acuna Alaya H, 2003, DNA damage in nasal and brain tissue of cannies exposed to air pollutant is associated with evidence of chronic brain inflammation and neuro degeneration, Toxocol Pahol 31: 524-38.

[19] Kattimani S, Mahadevan S. Treating children with attention-deficit/hyperactivity disorder and comorbid epilepsy. Annals of Indian Academy Of Neurology. 2011; 14(1):9.

[20] Sultana, S, Maithily K. Correlation between diet and attention deficit hyperactive disorder in children. Journal of international academic research for multidisciplinary. 2(4):351–9.

[21] Reilly CJ. Attention deficit hyperactivity disorder (ADHD) in childhood epilepsy. Research in Developmental Disabilities. 2011; 32(3):883–93.

[22] Hermann B, Jones J, Dabbs K, Allen Ca, Sheth R, Fine J, et al. The frequency, complications and aetiology of adhd in new onset paediatric epilepsy. Brain. 2007;130(12):3135–48.

[23] Das JP, Melnyk L. Attention checklist: a rating scale for mildly mentally handicapped adolescents. Psychological Reports. 1989; 64(3c):1267–74.

[24] Pliszka Sr. Patterns of psychiatric comorbidity with attention-deficit/hyperactivity disorder. Child and Adolescent Psychiatric Clinics of North America. 2000; 9:525–54.

[25] Chantiluke K, Christakou A, Murphy CM, Giampietro V, Daly EM, Ecker C, et al. Disorder-specific functional abnormalities during temporal discounting in youth with attention deficit hyperactivity disorder (ADHD), autism and comorbid ADHD and autism. Psychiatry

Research: Neuroimaging. 2014; 223(2):113–20.

[26] Goldstein S, Schwebach AJ. The comorbidity of pervasive developmental disorder and attention deficit hyperactivity disorder: results of a retrospective chart review. Journal of Autism And Developmental Disorders. 2004; 34(3):329–39.

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RESEARCH ARTICLE

STUDY ON PERCEPTION OF PHYSICIANS TOWARDS ADVERSE DRUG REACTION REPORTING - A SURVEY IN INDIA

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Abstract:

Background:

Ongoing assessment for a positive risk–benefit profile of any medicinal product is an important aspect of lifecycle management; it is also a regulatory requirement. Important stakeholders in this process of pharmacovigilance (PV) are the patients, healthcare practitioners, pharmaceutical companies and regulatory agencies. Despite the regulations for post-marketing drug safety monitoring being well-defined, the rate of reporting of adverse drug reaction (ADR) by the healthcare community continues to be inordinately low.

Objective:

To understand the awareness of and patterns of ADR reporting amongst healthcare practitioners in a major city of India.

Materials and methods:

This was a questionnaire-based cross-sectional survey involving 53 physicians of various specialties from Ahmedabad. Data collected was analysed descriptively to evaluate the awareness and understanding of physicians on ADR reporting.

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Results:

About 68% of the participating physicians were unaware of the PV reporting requirements or regulations in the country. Only 5.67% prescribers had reported a drug-related event at least once to the nearest ADR monitoring centre in the last six months from this survey.

Conclusion:

Underreporting of ADR is a major concern for the success of the PV program in India, which directly impacts public health. Spontaneously reported ADRs (SADRs) is the most commonly used methodology to gather data on a drug's safety profile. For the number of SADR to realistically reflect the observed ADRs in practice, a greater thrust in bringing awareness amongst the medical community on PV requirements and available infrastructure is the need of the hour.

Keywords- Pharmacovigilance, physicians, spontaneous reports, India

INTRODUCTION

Spontaneous reporting of adverse events (AEs) by the healthcare practitioners, the patient or caregiver is the most widely used and recommended tool to monitor the safety of a marketed medicines. Data form the USFDA lists Adverse drug reactions (ADRs) popularly known as side effects as the 4th leading cause of death in the developed world. Adverse drug reactions (ADRs) not only account for market withdrawals but also for changes in labels or introduction of new-labeled warnings for prescription drugs. (1)

While the drug may have undergone extensive clinical testing during development and its safety profile largely known, the very nature of it being done on a limited number of patients in controlled trial conditions precludes many of the rare AEs being detected. Once marketed, medicines are not used under the same conditions as clinical trials. They are used by a larger number of patients across a range of age groups, who have varied lifestyles, comorbid conditions, or are taking several medicines simultaneously. Common and predictable side effects are characterized during the development phase of the drug, but idiosyncratic or rare side effects may only be known once the medicine is used by a large number of patients under actual conditions of use. In addition, some side effects might not get discovered until the medicine has been used over a long period of time or even after stopping treatment. It is therefore imperative that the safety of medicines is monitored even after they are marketed so as to identify any formerly unknown information on side effects and, if required, vital action can be taken to protect public health.

The process of reviewing the safety of medicines following their authorization is known as Pharmacovigilance [2]. India, which is also one of the members of the WHO Programme for International Drug Monitoring has a formal system of Pharmacovigilance run as the Pharmacovigilance programme of India (PvPI) under whose aegis ADR monitoring centres have been set up across the country to monitor medicinal safety [3]. One of the ways regulatory authorities monitor the safety of medicines is by collecting and analysing spontaneous reports of suspected side effects from health professionals, patients or consumers called 'spontaneous adverse drug reaction reports' (SADR) [2]. The success of this widely used and recommended method is totally dependent on the contribution of health professionals and consumers to ensure that the observed side effects are adequately reported and recorded for analysis. In reality the program is plagued by underreporting in most parts of the world were such initiatives are run. WHO recommends a reporting rate of 200 events per million people per year as being adequately representative; most developed countries have a reporting rate of 130 and India around 40. While the reporting rate of SADRs in India has significantly gone up in the last few years, it contributes to less than 2% of the reported events in VigiBase, the WHO global safety data base hosted by Uppsala Monitoring Centre, and is disproportionate to the country's vast population and medicine consumption.

Underreporting of SADRs by physicians is considered one of the major obstacles in the success of the Pharmacovigilance Programme of India; thus having a negative impact on the public health [4]. Hence the present study was undertaken to evaluate the perception of physicians towards ADR reporting in India, and their awareness towards available resources.

MATERIALS AND METHODS

A questionnaire-based cross-sectional survey was performed for this study. The study questionnaire was designed and pre-validated with clinical practitioners on the answerability and information value of the questions Knowledge and perception based questionnaire (containing 9 questions was designed to obtain the information about knowledge regarding ADR reporting system in India and perception of ADR reporting (Appendix-1). More than one answer was allowed in some questions.

In the first question, the participating physicians were inquired about the average number of patients they had examined in last 6 months and in the second about the number of side effects seen amongst these. The response to the first two questions was based of their day-to-day practice. The next question sought their response on the usual course of action if a drug related AE was encountered and this included the option of changing medication, reducing the dose, informing the patient or reporting possibilities. The succeeding two questions were perception based asking about physician's choice on recipient of their ADR reporting information whether they would report to pharmacist, medical representative and senior medical

representative or nearest PV cell. The other question was asked to them on the ideal way according to them to manage these AEs by options like informing the patient and managing the event, informing the company and/or informing the regulatory authority. The practitioners were also asked about the number of ADRs they have reported in last 6 months and if reported, to whom, Medical representative or the regulatory authority (PV cell). And the last three questions were knowledge based inquiring whether the physician knew about the location of the nearest PV cell, and reporting mode options (phone, fax, e-mail, in person, Not Applicable) if they report to a PV cell and the minimum requirements to report an ADR.

The study population surveyed involved medical practitioners from varied specialties from Ahmedabad. A total of 60 questionnaires were distributed to medical doctors, excluding the practitioners involved in the pre-validation. Those who were not willing to participate or did not return the questionnaire within the given time were excluded from the study. The completion of the questionnaire by respondents was taken as their consent to participate in the study. Hence, out of 60 questionnaires, only 53 were taken into consideration.

The information was recorded and analysed using simple descriptive statistics with use of graphs and figures to interpret and report the results of this survey. In order to preclude any potential bias, the disclosure of name of the responder was made optional.

RESULTS

Total of 53 responses were taken into consideration for this survey from Ahmedabad, which is one of the larger cities in India. All the responders were practitioners from various medical specialties including family physicians, consultant physicians, paediatricians, dermatologists, gynaecologists, E.N.T specialists, ophthalmologists, neurologists, critical care and emergency medicine specialists, anaesthetists, cardiologists and pulmonologists.

Over the past 6 months, 41.51% of the doctors had seen more than 500 patients 33.96% practitioners had consulted around 200 - 500 patients; 15.10% doctors examined 100-200 patients and rest of the physicians had about 50-100 patients [Table 1].

For the surveyed physicians, 30% doctors observed more than 6 cases of suspected AE in the last six months, 26.42% doctors observed 2 to 5 cases of ADRs, while the rest of the group (43.40%) did not observe more than 1 ADR [Table 2].

Table 1: Average number of patients seen and number of side effects encountered by practitioners in last 6 months.

Parameter	Range	Response	% Response
(A) No. of patients seen	50-100	5	9.43
	101-200	8	15.10
	201-500	18	33.96
	More than 500	22	41.51
(B) No. of side effects encountered	0-1	23	43.40
	2-5	14	26.42
	6-10	8	15.10
	More than 10	8	15.10

Table 2:- Opinion on ideal way of handling these events.

Way to Handle These Events	Response	% Response
Informing the patient and managing the event	23	43.40
Informing the patient and managing the event + Informing the company	7	13.21
Informing the patient and managing the event + Informing the company + Informing the regulatory authority	23	43.40

The action taken in response to the adverse effects for most of them was replacing or modifying treatment [Chart 1]; and doctors had different preferences for reporting ADRs [Chart 2]; less than 4% responded that they would report the event to the PV cell [Chart 3].

The awareness of the nearest PV cell or the available of modes of reporting as well knowledge on the minimum requirements of reporting were lacking amongst the larger number of respondents.

Out of 53, 36 practitioners were totally unaware about the location of the nearby PV cell. 43% of the practitioners were ignorant about the means by which they can report an ADR; an additional 17% thought it is necessary to report the ADR in person [Chart 4].

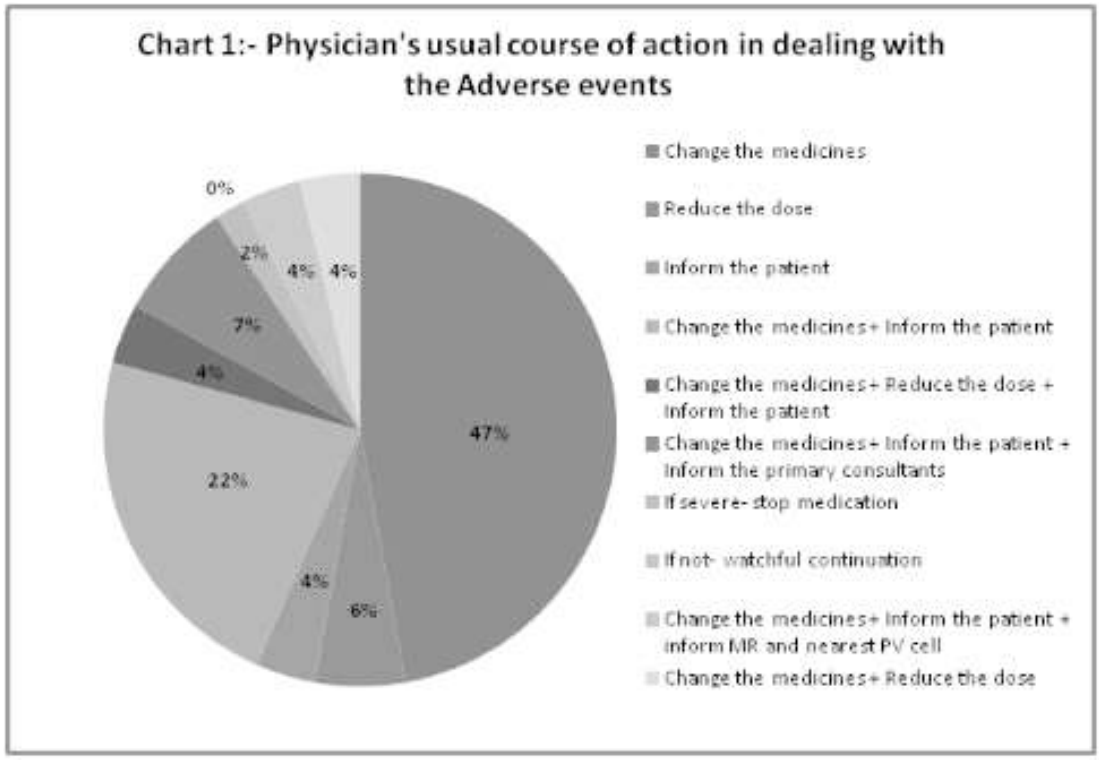


Chart 1:- Physician's usual course of action in dealing with the Adverse events
47%
6%
4%
22%
4%
7%
2%
4%
4%
0%
Change the medicines
Reduce the dose
Inform the patient
Change the medicines+ Inform the patient
Change the medicines+ Reduce the dose + Inform the patient
Change the medicines+ Inform the patient + Inform the primary consultants
If severe- stop medication
If not- watchful continuation
Change the medicines+ Inform the patient + inform MR and nearest PV cell
Change the medicines+ Reduce the dose

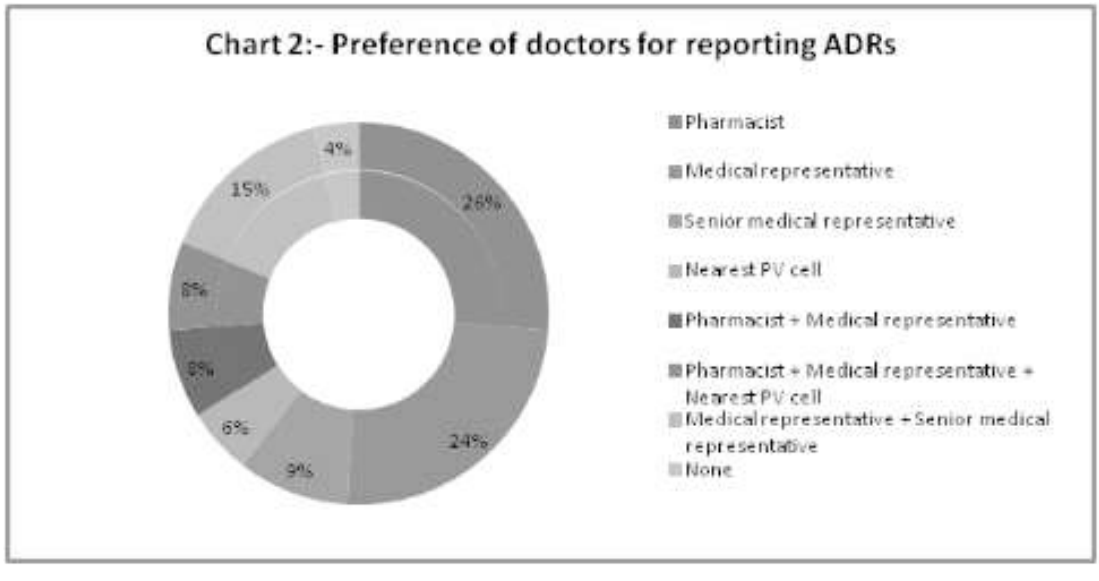
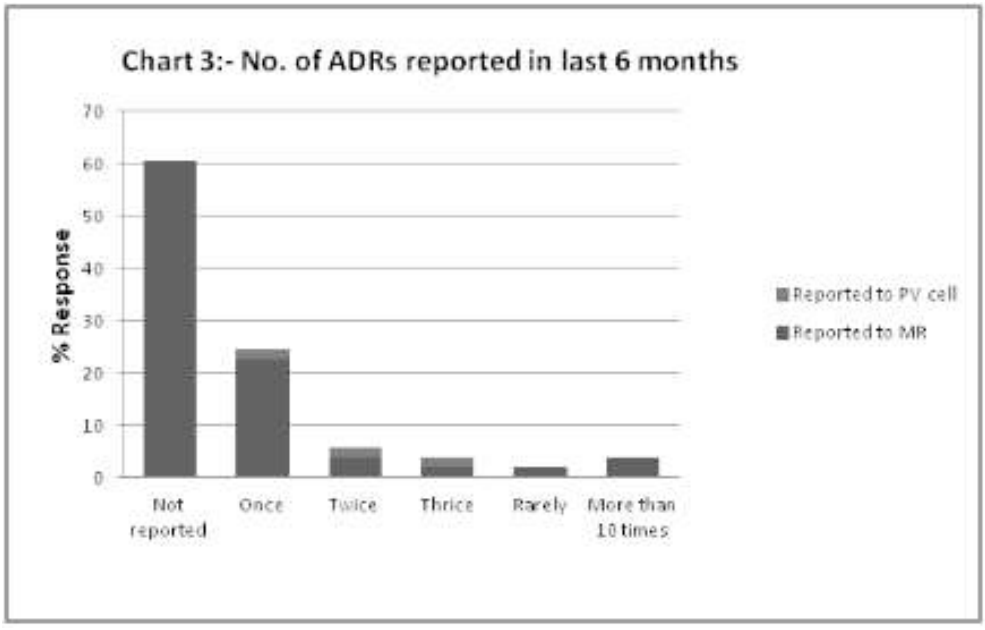
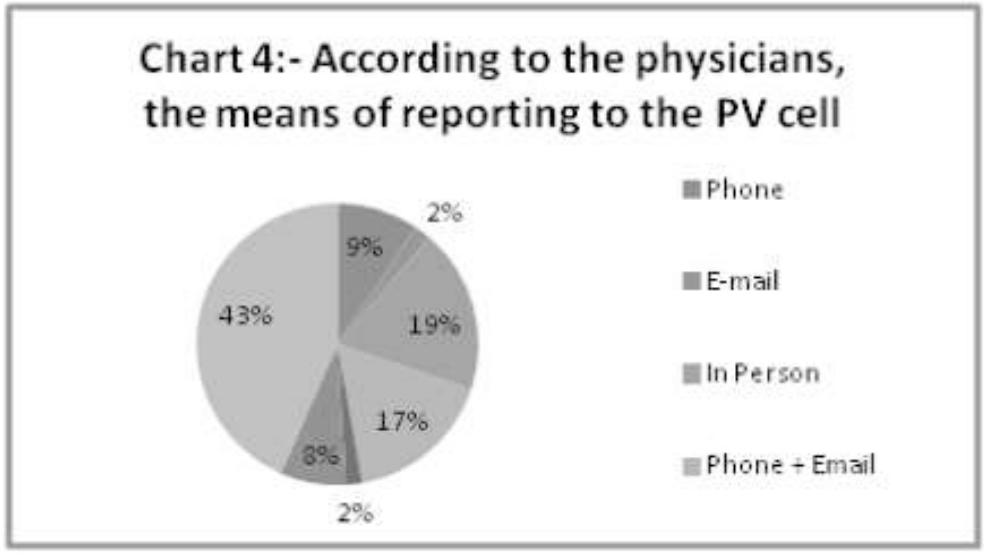


Chart 2:- Preference of doctors for reporting ADRs
26%
24%
9%
6%
9%
6%
15%
4%
Pharmacist
Medical representative
Senior medical representative
Nearest PV cell
Pharmacist + Medical representative
Pharmacist + Medical representative + Nearest PV cell
Medical representative + Senior medical representative
None





Also the minimum requirements to report an ADR were unknown to 77.36% physicians. According to several of the physicians, observation of rash, itching, breathing difficulties, severe life threatening/anaphylactic ADR were the reporting requirements for an ADR.

DISCUSSION AND CONCLUSION

Globally, drug regulators are placing increased thrust on robust safety monitoring mechanisms for pharmacovigilance. The PvPI program of India has also taken great strides in this regard with the National Coordination

Centre in Ghaziabad and zonal offices as well as almost 150 ADR monitoring cells around the country.

A dedicated help line number, a web-based ADR reporting form and a mobile application form easily available modes of reporting suspected ADRs to the health authority. These ADRs once reported and assessed are further data based in the WHO repository Vigibase, thus not only adding value on safe guarding national health but contributing to global efforts in PV.

However, the overall strength of any system lies in its weakest link. Multiple studies and repeatedly demonstrated the low reporting rates of ADR form the healthcare and patient communities. (5, 6, 7, 8)

Our survey with its limited regional population corroborated these findings with majority of respondents, who were all practicing physicians being inadequately unaware of the need of watchful assessment and reporting.

Studies earlier than ours have cited various reasons for this phenomenon, which include complacency, insecurity and legal issues, case series publication, diffidence, professional responsibility, lethargy and financial incentives to report. The results in our survey point to lack of awareness and knowledge on pharmacovigilance amongst our respondents. (5, 6, 7, 8)

These include their own responsibility to detect and report, the minimum requirements of reporting, and the existence of the PVPI function.

Training and awareness program amongst the medical community on the needs of PV, their own reporting responsibilities, the structure and functioning of PVPI and information on the minimum requirements of ADR reporting is the need of the hour to ensure the PVPI mission of protecting national health form adverse effects of medicines can indeed be upheld.

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REFERENCES

1. Siramshetty VB, Nickel J, Omieczynski C, Gohlke BO, Drwal MN, Preissner R. WITHDRAWN--a resource for withdrawn and discontinued drugs.Nucleic Acids Res. 2016;44(D1):D1080-6.

2. New EU pharmacovigilance legislation- key concepts, European Medicine Agency, 2013. [Last accessed on 1st July, 2013] Available from: http://www.ema.europa.eu/docs/en_GB/documents_library/Other/2012/07/ WC500129593.pdf

3. Pharmacovigilance program of India, 2010. CDSCO, Ministry of Health and Family Welfare, Government of India. 2010. [Last accessed on 1st

July, 2013]: Available from: http://cdsco.nc.in/pharmacovigilance.htm

4. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009;32(1):19-31.

5. Kamtane R, Jayawardhani V. Knowledge, attitude and perception of physicians towards adverse drug reaction (ADR) reporting: A pharmacoepidemiological study. Asian J Pharm Clin Res 2012;5(3):210–214

6. Khan SA, Goyal C, Chandel N, Rafi M. Knowledge, attitudes, and practice of doctors to adverse drug reaction reporting in a teaching hospital in India: An observational study. J Nat Sci Biol Med. 2013;4(1):191-6.

7. Lihite RJ, Lahkar M. An update on the Pharmacovigilance Programme of India. Front Pharmacol. 2015;6:194.

8. Sabblah G, Akweongo P, Darko D, Dodoo ANO, Sulley AM. Adverse Drug Reaction Reporting by Doctors in a Developing Country: A Case Study from Ghana. Ghana Med J. 2014 Dec; 48(4): 189–193.

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[1] Merkel TJ, Jones SW, Herlihy KP, Kersey FR, Shields AR, Napier M, Luft JC, Wu H, Zamboni WC, Wang AZ, Bear JE, DeSimone JM. Using mechanobiological mimicry of red blood cells to extend circulation times of hydrogel microparticles. *Proc. Natl. Acad. Sci.*, 2010, 108:586-591.

Chapter in a book: Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors:The genetic basis of human cancer. New York: McGraw-Hill; 2002, pp. 93-113.

Book: Getzen TE. Molecular cell biology. 3rd ed. New York: Scientific American 1995, pp.102-104.

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