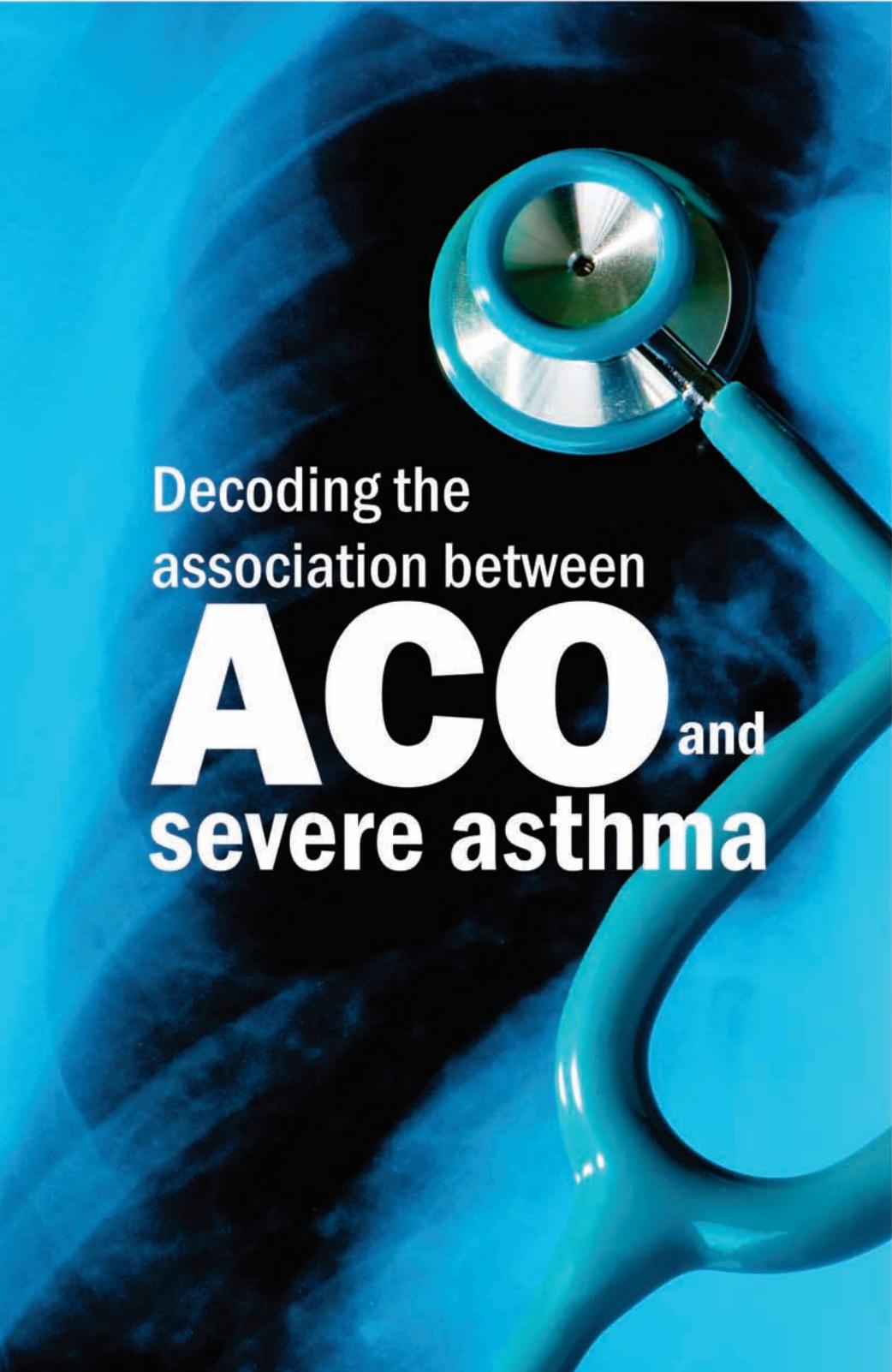


MEDICINE UPDATE

 Passi HealthCom



Decoding the
association between
ACO and
severe asthma

Volume 27
Number 4
August 2019



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Contents

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Sarvesh Passi

EDITORIAL

Anti-diabetic drugs - The future landscape

7

SECTION 1

Global Update

Adolescent educational outcomes associated with early childhood nutrition

10

Nutritional status of children in India based on household socio-economic condition

10

Effectiveness and safety of levetiracetam in comparison to other conventional antiepileptic drugs

11

Use of levetiracetam as a first-line antiepileptic agent during pregnancy in Indian women with epilepsy

11

Variation in the prevalence of ACO defined by different diagnostic criteria

11

Appraising the expediency of neutrophil gelatinase-associated lipocalin as a complementary biomarker for ACO

12

SECTION 2

Clinical Update

Decoding the association between ACO and severe asthma

13



✗ Allergic Cough

✗ Smoker's Cough

✗ Drug Induced Cough

✗ Cough with RTI

✗ Cough with Bronchial Asthma and Bronchitis

✗ Cough with LPRD/GERD*

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Contents

ADVISORY BOARD

A.K. Agarwal	Administration of sevelamer in a hemodialysis patient with hyperphosphatemia	18
Naresh Trehan	An elderly female with benign paroxysmal positional vertigo managed with high-dose betahistine therapy for 3 months	20
S.K. Sarin	Challenges and treatment considerations in women with epilepsy: A review	24
Tamal K. Biswas	Endothelial effects of sevelamer: Beyond the basics	27
K.B. Gupta	Recent advances in management of neonatal seizures: Levetiracetam as first-line pharmacotherapy	30
A.P. Jain		
K.V. Krishna Das		
M. Panja		
Prasant Kumar Sahoo		
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M.M. Singh		
Virendra Singh		
Subhash Varma		
Vijaikumar		
S. Chandrasekharan		
V. Parameshwara		
Sukhvinder Singh		

SECTION 3

Medical Quiz

33

SECTION 4

Events Update

34

SECTION 5

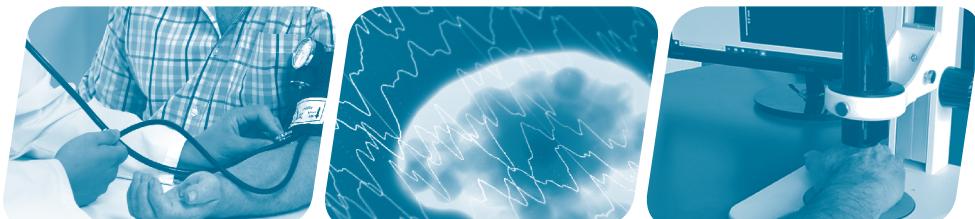
Tech Update

35

SECTION 6

Legal Update

37



EDITORIAL

ANTI-DIABETIC DRUGS - THE FUTURE LANDSCAPE

Dr. A. K. Baliarsinha
MBBS, MD, DM (Endocrinology)
Professor and head,
Dept. of Endocrinology,
SCB Medical College, Cuttack, Odisha

Diabetes mellitus is the most common metabolic and endocrine disorder affecting the entire world and it continues to grow at an alarming rate. As per a recent estimate, around 425 million people suffer from diabetes in 2017 and the number is predicted to rise beyond 649 million by 2045.¹ Majority (around 90%) of them being Type 2 diabetes mellitus (T2DM).² The disease poses a tremendous health challenge and burden on both affected individuals as well as the healthcare delivery system. The field of drug discovery in diabetes has grown by leaps and bounds in recent decades and now we have multiple agents approved for treatment for T2DM. But despite this fact, more than a third of patients with diabetes do not achieve or maintain an appropriate glycemic target with currently used drugs.³ The drug therapy becomes further challenging and complex in the setting of poor response to multiple oral anti-diabetic drugs (due to progressive beta-cell failure over time), frequent multiple chronic complications of diabetes itself and potential drug interactions with other drugs prescribed for other comorbidities. Hence, current research is directed towards development of novel drugs which are efficacious, safe and can retard these complications of T2DM. Newer therapies are directed towards novel targets which are dysregulated in T2DM and are not currently addressed.

Current class of anti-diabetic drugs in clinical practice include biguanides, sulphonylureas, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, sodium dependent glucose co transporter (SGLT-2) inhibitors, dopamine agonists, bile acid sequestrants, insulin and its analogues, amylin agonist and glucagon like peptide 1 (GLP 1) analogues. Different combinations of drugs are used for glycemic control but failure of glycemic control ensues over period of time and insulin is required in many individuals for optimal glycemic control. Hypoglycemia risk poses special clinical challenge during intensification of anti-diabetic drugs especially insulin and secretagogues. Hence, there is an unmet need of developing newer anti-diabetic drugs which will help in optimizing glycemic control albeit with minimal hypoglycemia and significant extra-glycemic beneficial effects.

Several investigational agents are being developed and tested for mitigating β -cell dysfunction in T2DM. These agents target novel sites in pancreatic β -cell and hence augment insulin secretion. Certain G-protein coupled receptors (GPR) expressed in beta cell are activated by fatty acids, leading to augmentation of insulin secretion. Hence, certain ligands like GPR 40 and GPR 119 agonists are tested for enhancing insulin secretion through this mechanism without actually entering the β -cell.^{4,5} Apart from that, GPR119 agonists also enhance GLP1 production and hence the incretin response, as these receptors (GPR119) are also expressed in other enteroendocrine cells like K and L cells.⁶ Glucokinase is a key enzyme and acts as a glucose sensor in beta-cell. Agents which activate the glucokinase enzyme and hence increase insulin secretion and hepatic glucose metabolism simultaneously are being developed.^{7,8} These agents referred as glucokinase activators have shown modest glycemic lowering capacity for 4-6 months, but subsequent efficacy reduced.⁸ Liver specific glucokinase activators are now being developed to offset hyperglycemic side effect of these drugs.⁷ A novel molecule (Imeglimin) which is a triazine derivative that not only enhances insulin secretion but also modulates mitochondrial energetics to increase insulin sensitivity has been tried in management of T2DM. Though studies are very few, but this agent has been shown to be efficacious alone or in combination with other oral antidiabetic drug in achieving glycemic control.^{9,10}

The past decade has seen the emergence of a new class of drugs that is the incretin mimetics. Due to its glucose dependent action, they have established themselves as safer and efficacious alternatives to other oral antidiabetic drugs. Various GLP1 analogues and DPP IV inhibitors are currently available in clinical practice for last few years. However, in recent past, fixed dose combination of a basal insulin and a GLP-1 analogue have been introduced (combination of liraglutide with insulin degludec and combination of lixisenatide with insulin glargine).^{11,12} These novel combinations have shown good glycemic control with favorable effects on weight change and hypoglycemia incidence.¹¹⁻¹³ All of currently available GLP1 analogues are either once daily or once weekly injectable preparations. An orally active GLP1 analogue (semaglutide) has shown good glycemic control in preliminary phase 2 study and is now being evaluated in a larger phase 3 study.¹⁴ Newer innovations in domain of incretin mimetics include development of an implanted subcutaneous mini-pump (ITCA 650) which

delivers upto 80 μ g of exenatide daily and an exenatide once-monthly suspension.^{15,16} The other major group of incretin mimetics are the oral DPP IV inhibitors which has to be taken daily. Two newer molecules, omarigliptin and trelagliptin, have been developed as an once weekly DPP IV inhibitors and they have shown to be efficacious in clinical studies.^{17,18}

Inhibitors of the enzyme 11-beta hydroxysteroid dehydrogenase I (11- β HSD-I) which is responsible for generation of active cortisol from inactive cortisone have been tried in management of T2DM with some benefits in phase 2 study.¹⁹ However, long term efficacy and safety study are currently lacking. Two novel metabolic targets for glycemic control include enzymes glycogen phosphorylase and protein tyrosine phosphatase IB (PTB IB). Inhibition of the first enzyme has been shown to improve glycemia in mice studies.²⁰ However, effects of these drugs on long term basis and influence of exercise activities remain to be seen.²¹ Similarly, PTB IB inhibition has shown to improve glycemic status, insulin sensitivity in animal studies.²² Various adipokines like leptin and adiponectin have been evaluated for their role in glycemic management.²³⁻²⁵ Analog of Fibroblast growth factor 21(FGF21), a peptide synthesized by adipose tissue, liver and muscle has been shown to improve insulin resistance and lipid profile in humans.²⁶ Adenosine monophosphate kinase (AMPK) is the key energy sensor of cell. Metformin is known to exert its effect via this pathway. This enzyme promotes energy production via increased glucose uptake and increased fatty acid oxidation. Hence, AMPK activators are developed as a therapeutic tool for management of T2DM.²⁷

One major class of drugs which have been a late addition to anti-diabetic armamentarium but shown considerable promise in diabetes care, are the class of SGLT2 inhibitors. Several molecules of this class have shown significant benefit in terms of extra glycemic effects. Empagliflozin has shown to reduce adverse cardiovascular event in recently concluded EMPAREG trial.²⁸ Many other SGLT2 inhibitors are currently in advanced stage of development.²⁹ A novel dual SGLT1 and SGLT2 inhibitor, sotagliflozin, has shown similar efficacy in terms of glycemic control in comparison to other SGLT2 inhibitors in clinical trial.³⁰ We know that the peroxisome proliferator-activated receptor γ (PPAR γ) agonist pioglitazone use is associated with fluid retention and worsening of congestive heart failure despite its beneficial effect on glycemic control. A selective PPAR γ modulator (INT131) has been developed and it has

shown to improve glucose metabolism while minimizing the side effects of full PPAR γ agonists (pioglitazone).³¹

There also has been tremendous advancements in development of newer formulations and delivery systems of insulin therapy. Some of these include fast-acting insulin aspart, Bio Chaperone ultra-rapid-acting insulin, inhaled insulin, oral insulin spray and smart insulin.³²

Hence, the future of anti-diabetic drugs research is definitely exciting and we may see emergence of new drugs which could meet these currently unmet needs of diabetes care. Despite the progress in various drug developments discussed above, it remains to be seen how many of these agents actually see the end of tunnel and become available for clinical use.

REFERENCES

- International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017.
- World Health Organization. Global Report on Diabetes. Geneva: World Health Organization, 2016.
- De Pablos-Velasco P, Parhofer KG, Bradley C, Eschwege E, Gönder-Frederick L, Maheux P, et al. Current level of glycaemic control and its associated factors in patients with type 2 diabetes across Europe: data from the PANORAMA study. *Clin Endocrinol (Oxf)* 2014;80:47–56.
- Mancini AD, Poitout V. GPR40 agonists for the treatment of type 2 diabetes: life after 'TAKing' a hit. *Diabetes Obes Metab* 2015;17:622–29.
- Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* 2014;383:1068–83.
- Ohishi T, Yoshida S. The therapeutic potential of GPR119 agonists for type 2 diabetes. *Expert Opin Investig Drugs* 2012;21:321–28.
- Clifford J Bailey, Abd A Tahran, Anthony H Barnett. Future glucose-lowering drugs for type 2 diabetes. *Lancet Diabetes Endocrinol* 2016;4:350–59.
- Nakamura A, Terauchi Y. Present status of clinical deployment of glucokinase activators. *J Diabetes Investig* 2015;6:124–32.
- Pirags V, Lebovitz H, Fouqueray P. Imeglimin, a novel oral antidiabetic, exhibits a good efficacy and safety profile in type 2 diabetic patients. *Diabetes Obes Metab* 2012;14:852–8.
- Fouqueray P, Pirags V, Diamant M, Schernthaler G, Lebovitz HE, Inzucchi SE, et al. The efficacy and safety of imeglimin as add-on therapy in patients with type 2 diabetes inadequately controlled with sitagliptin monotherapy. *Diabetes Care* 2014;37(7):1924–30.
- Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus Lixisenatide, versus insulin glargin and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. *Diabetes Care* 2016;39:2026–2035.
- Linjawi S, Bode BW, Chaykin LB, Courrèges JP, Handelsman Y, Lehmann LM, et al. The efficacy of IDegLira (insulin degludec/liraglutide combination) in adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist and oral therapy: DUAL III randomized clinical trial. *Diabetes Therapy* 2017;8(1):101–14.
- Virginia Valentine, Jennifer Goldman, Jay H. Shubrook. Rationale for Initiation and Titration of the Basal Insulin/GLP-1RA Fixed-Ratio Combination Products, IDegLira and IGlarLixi, for the Management of Type 2 Diabetes. *Diabetes Ther* 2017;8(4):739–752.
- Novo Nordisk A/S. Efficacy and Long-term Safety of Oral Semaglutide Versus Sitagliptin in Subjects With Type 2 Diabetes (PIONEER 3) [accessed 2017 Nov 14] Available from: <https://clinicaltrials.gov/ct2/show/NCT02607865>.
- Henry RR, Rosenstock J, Logan D, Alessi T, Luskey K, Baron MA. Continuous subcutaneous delivery of exenatide via ITCA 650 leads to sustained glycemic control and weight loss for 48 weeks in metformin-treated subjects with type 2 diabetes. *J Diabetes Complications* 2014;28: 393–98
- Wysham CH, MacConnell L, Hardy E. Efficacy and Safety of Multiple Doses of Exenatide Once-Monthly Suspension in Patients With Type 2 Diabetes: A Phase II Randomized Clinical Trial. *Diabetes care* 2016;39(10):1768–76.
- Goldenberg R, Gantz I, Andryuk PJ, O'Neill EA, Kaufman KD, Lai E, et al. Randomized clinical trial comparing the efficacy and safety of treatment with the once-weekly dipeptidyl peptidase-4 (DPP-4) inhibitor omarigliptin or the once-daily DPP-4 inhibitor sitagliptin in patients with type 2 diabetes inadequately controlled on metformin monotherapy. *Diabetes Obes Metab* 2017;19:394–400.
- Inagaki N, Onouchi H, Maezawa H, Kuroda S, Kaku K. Once-weekly trelagliptin versus daily alogliptin in Japanese patients with type 2 diabetes: a randomised, double-blind, phase 3, non-inferiority study. *Lancet Diabetes Endocrinol* 2015;3(3):191–7.
- Rosenstock J, Banarer S, Fonseca VA, Inzucchi SE, Sun W, Yao W, et al. The 11-β-hydroxysteroid dehydrogenase type 1 inhibitor INCB13739 improves hyperglycemia in patients with type 2 diabetes inadequately controlled by metformin monotherapy. *Diabetes Care* 2010; 33: 1516–22.
- Martin WH, Hoover DJ, Armento SJ, Stock IA, McPherson RK, Danley DE, et al. Discovery of a human liver glycogen phosphorylase inhibitor that lowers blood glucose in vivo. *Proc Natl Acad Sci USA* 1998;95:1776–1781.
- Baker DJ, Timmons JA, Greenhaff PL. Glycogen phosphorylase inhibition in type 2 diabetes therapy: a systematic evaluation of metabolic and functional effects in rat skeletal muscle. *Diabetes* 2005;54:2453–2459.
- Johnson TO, Ermolieff J, Jirousek MR. Protein tyrosine phosphatase 1B inhibitors for diabetes. *Nat Rev Drug Discov* 2002;1:696–709.
- Coppari R, Bjørbaek C. Leptin revisited: its mechanism of action and potential for treating diabetes. *Nat Rev Drug Discov* 2012;11:692–708.
- Fisman EZ, Tenenbaum A. Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? *Cardiovasc Diabetol* 2014;13:103–09.
- Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami KI, Matsuda K, et al. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. *Nature* 2013;503:493–99.
- Gaich G, Chien JY, Fu H, Glass LC, Deeg MA, Holland WL, et al. The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes. *Cell Metab* 2013;18(3):333–40.
- Coughlan KA, Valentine RJ, Ruderman NB, Saha AK. AMPK activation: a therapeutic target for type 2 diabetes? *Diabetes Metab Syndr Obes* 2014;7:241–53.
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373(22):2117–28.
- Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. *Drug Des Devel Ther* 2014;8:1335–80.
- Lampueta P, Zambrowicz B, Strumph P, Sands A. Development of sotagliflozin, a dual sodium-dependent glucose transporter 1/2 inhibitor. *Diabetes Vas Dis Res* 2015;12:101–10.
- DePaoli AM, Higgins LS, Henry RR, Mantzoros C, Dunn FL, and the INT131-007 Study Group. Can a selective PPAR γ modulator improve glycemic control in patients with type 2 diabetes with fewer side effects compared with pioglitazone? *Diabetes Care* 2014;37:1918–23.
- Cahn A, Miccoli R, Dardano A, Del Prato S. New forms of insulin and insulin therapies for the treatment of type 2 diabetes. *Lancet Diabetes Endocrinol* 2015;3:638–52.

SECTION 1

GLOBAL UPDATE

ADOLESCENT EDUCATIONAL OUTCOMES ASSOCIATED WITH EARLY CHILDHOOD NUTRITION

An estimated 200 million children of less than 5 years of age—most of whom live in South Asia and sub-Saharan Africa—fail to achieve their potential primarily because of undernutrition. Undernutrition during the first 1000 days of life is associated with lower survival and higher incidence of acute and chronic diseases in later life, reduced cognitive skills, fewer schooling grades, lower economic productivity, lower birth weight and shorter children in the next generation. More than half—almost 60 million—of the world's underweight children aged less than 5 years are Indian). The proportion of Indian children who are stunted or underweight declined from 48% and 43%, respectively, in 2005–2006 to 39% and 30% in 2013–2014. However, the prevalences vary considerably across states and districts. In the poorer states of Bihar, Jharkhand, Madhya Pradesh, Orissa, Rajasthan, and Uttar Pradesh, 58.8% and 43.3% of children were still stunted and underweight, respectively, in 2011.

The Integrated Child Development Scheme (ICDS) program of India, launched in 1975 and universalized in 2008–2009 has the potential to reduce India's undernutrition burden. It is also the world's largest maternal and child health program. It is designed to address nutritional and developmental needs of children below 6 years of age, pregnant women, and nursing mothers.

Source: Nandi A, Ashok A, Kinra S, Behrman JR, Laxminarayan R. Early Childhood Nutrition Is Positively Associated with Adolescent Educational Outcomes: Evidence from the Andhra Pradesh Child and Parents Study (APCAPS) [published online ahead of print, 2016 Mar 9]. *J Nutr.* 2016;146(4):806–813.



NUTRITIONAL STATUS OF CHILDREN IN INDIA BASED ON HOUSEHOLD SOCIO-ECONOMIC CONDITION

Growing evidence suggest there exists a socio-economic gradient of childhood malnutrition in India. Using National Family Health Survey-3 data, an attempt was made to estimate socio-economic inequality in childhood stunting at the state level through concentration index (CI). Across the states, a disproportionate burden of stunting was observed among the children from poor SES, more so in urban areas. The state having lower prevalence of chronic childhood malnutrition showed much higher burden among the poor. Though a negative correlation ($r = -0.603$, $p < .001$) was established between net state domestic product (NSDP) and CI values for stunting. In spite of the declining trend of chronic childhood malnutrition in India, the concerns remain for its disproportionate burden on the poor. The socio-economic gradient of long-term nutritional status among children needs special focus, more so in the states where chronic malnutrition among children apparently demonstrates a lower prevalence. The paper calls for state specific policies which are designed and implemented on a priority basis, keeping in view the nature of inequality in childhood malnutrition in the country and its differential characteristics across the states.

Source: Kanjilal B, Mazumdar PG, Mukherjee M, Rahman MH. Nutritional status of children in India: household socio-economic condition as the contextual determinant. *Int J Equity Health.* 2010;9:19.

EFFECTIVENESS AND SAFETY OF LEVETIRACETAM IN COMPARISON TO OTHER CONVENTIONAL ANTIEPILEPTIC DRUGS

The current review aimed at assessing the efficacy, tolerability and cost-effectiveness of levetiracetam in epilepsy management. Several scientific databases were searched for systematic reviews, meta-analyses, randomized controlled trials, observational studies, case reports and economic studies of levetiracetam published between January 2007 and April 2018.

Results demonstrated levetiracetam to be as effective as other antiepileptic agents such as carbamazepine, oxcarbazepine, lamotrigine and phenobarbital. In addition, levetiracetam was associated with low rates of intrauterine death, malformation and cognitive effects when administered in pregnant women. Discontinuation due to side-effects was reduced with levetiracetam as compared to carbamazepine.

These findings suggested that levetiracetam has an equal efficacy compared with other conventional antiepileptic drugs and it is relatively free of teratogenic side-effects.

Source: Yi ZM, Wen C, Cai T, et al. Levetiracetam for epilepsy: an evidence map of efficacy, safety and economic profiles. *Neuropsychiatr Dis Treat*. 2018;15:1-19.

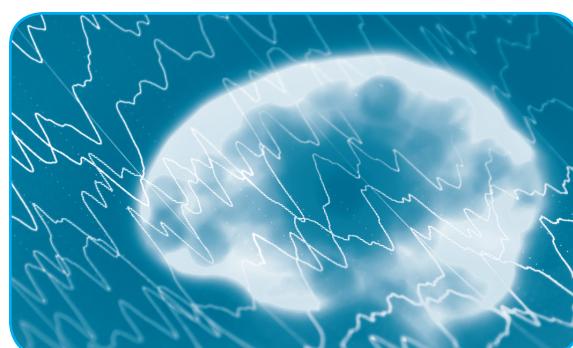
USE OF LEVETIRACETAM AS A FIRST-LINE ANTIEPILEPTIC AGENT DURING PREGNANCY IN INDIAN WOMEN WITH EPILEPSY

A study was conducted in a group of Indian women with epilepsy to determine the effectiveness and safety of levetiracetam during pregnancy. Data of 99 pregnant women with epilepsy undergoing evaluation at the department of obstetrics and gynecology at a tertiary care teaching hospital was retrospectively reviewed.

Women included in the study were subjected to receive different types of antiepileptic drugs such as carbamazepine (n=35), levetiracetam (n=28), valproate (n=15), phenytoin (n=13), oxcarbazepine (n=3), lamotrigine (n=3) and clobazam (n=2). Results demonstrated an increased risk of major congenital malformations with use of valproate (13.3%). In addition, the incidence of fetal distress was significantly higher with use of phenytoin as compared to levetiracetam ($p=0.003$). Furthermore, no congenital malformations were observed in neonates born to mothers administered levetiracetam during pregnancy.

Thus, the study findings demonstrated potential use of levetiracetam as a first-line antiepileptic drug during pregnancy with no risk of fetal malformations.

Source: Bansal R, Suri V, Chopra S, et al. Levetiracetam use during pregnancy in women with epilepsy: Preliminary observations from a tertiary care center in Northern India. *Indian J Pharmacol*. 2018;50(1):39-43.



VARIATION IN THE PREVALENCE OF ACO DEFINED BY DIFFERENT DIAGNOSTIC CRITERIA

Asthma-COPD overlap has been defined by various authorities and multiple definitions have been provided; however, the concordance between these definitions and other diagnostic criteria remains elusive. In this context, Barczyk and colleagues conducted a study to evaluate the concordance between different ACO definitions and to estimate the definition-based ACO prevalence and characteristics.

This was a prospective, real-life study based on a 32-item data set that was performed in a mixed population of patients with asthma and COPD and the investigators analyzed five different definitions of ACO, including the GINA/GOLD criteria. The results divulged the following:

- The final analysis included a total of 1609 patients
- On the whole, the level of agreement between different ACO definitions was poor
- Cohen kappa coefficient for the agreement between ACO definition by GINA/GOLD and other ACO definitions varied from 0.06 to 0.21. Only 2 patients (0.12%) complied with all the ACO definitions. Definition-based ACO

prevalence ranged from 3.8% (Spanish criteria) to 18.4% (clinician's diagnosis)

- A total of 573 (33.4%) patients fulfilled the criteria from at least 1 ACO definition. As much as 27.5% patients of the whole investigated group could not be classified as suffering from "pure" asthma, "pure" COPD, or ACO
- The most severe symptoms were detected in patients with ACO defined as COPD and asthma diagnosed at age <40 years.

Thus, findings of this study suggest that the current definitions of ACO identify distinct populations that share only a small number of common features and present with different disease phenotypes. In fact, there is considerable variation in the prevalence of ACO, depending on the definition applied.

Source: Barczyk A, Maskey-Warzęchowska M, Górska K, et al. Asthma-COPD Overlap-A Discordance Between Patient Populations Defined by Different Diagnostic Criteria. *J Allergy Clin Immunol Pract.* 2019; pii: S2213-2198(19)30395-2.



APPRaising THE EXPEDIENCY OF NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN AS A COMPLEMENTARY BIOMARKER FOR ACO

The lack of a standardized definition of ACO translates into a wide variation in its prevalence. Although the blood eosinophil count is considered a biomarker for identifying ACO, it lacks a distinct cut off value. In this context, a study was conducted to quantify plasma levels of neutrophil gelatinase-associated lipocalin (NGAL), a potential biomarker for distinguishing between ACO and non-ACO COPD and correlation of NGAL with the blood eosinophil count which has been widely accepted novel biomarker for ACO.

This was a Korean cohort in the COPD in dusty area (CODA) study that included 137 patients with COPD confirmed by spirometry. ACO was defined by a positive bronchodilator response ($FEV_1 >12\%$ and >200 mL from baseline) or based on a previous history of asthma. The results divulged the following:

- Seventy-seven of the 137 patients were ACO and 60 were non-ACO COPD
- There was no significant difference between the overall plasma NGAL levels in non-ACO versus ACO patients (15.9 ± 7.9 and 15.6 ± 6.6 ng/mL, respectively)
- However, NGAL levels were significantly higher in the ACO compared to the non-ACO group among female patients (17.0 ± 6.4 and 11.1 ± 4.5 ng/mL, respectively; $p=0.01$)
- Of note, NGAL levels, in female subjects, demonstrated a good predictive ability to distinguish between ACO and non-ACO COPD [area under the receiver operating characteristic curve (AUROC), 0.77]; the predictive ability was similar to that of the blood eosinophil count (AUROC, 0.79)
- There was a higher probability of differentiating ACO from non-ACO among patients in the highest tertile of NGAL levels (odds ratio, 1.72; p for trend =0.01).

This study demonstrated that elevated plasma levels of NGAL are associated with a higher likelihood of ACO, especially in females. Additionally, plasma NGAL levels corroborated with blood eosinophil count in distinguishing ACO patients.

Source: Jo YS, Kwon SO, Kim J, Kim WJ. Neutrophil gelatinase-associated lipocalin as a complementary biomarker for the asthma-chronic obstructive pulmonary disease overlap. *J Thorac Dis.* 2018;10(8):5047-5056.

SECTION 2

CLINICAL UPDATE

Decoding the association between ACO and severe asthma

ASTHMA-COPD OVERLAP: AN OVERVIEW

Asthma and COPD are highly prevalent chronic lung diseases with an associated high disease burden. Asthma, which is often allergic in origin, frequently begins in infancy or childhood with variable airflow obstruction and intermittent wheezing, cough, and dyspnea. Patients with COPD, in contrast, are usually current or former smokers who present after the age of 40 years with often-persistent symptoms including dyspnea and a productive cough. Thus, on the basis of age and smoking history, it is often easy to distinguish between asthma and COPD.

However, some patients have features compatible with both diseases, and are considered to have an asthma-COPD overlap (ACO).^{1,2}

Asthma, as an atopic disease, usually presents early onset with the typical Th2 lymphocytes-derived airway and systematic inflammation and good response to inhaled corticosteroids (ICS). On the other hand, COPD characterized by fixed airflow limitation, prefers to be a late-onset disease caused by enhanced Th1 inflammatory response to inhaled noxious particles or gases. ACO, sharing the mixed features of both, stands at the intersection of asthma and COPD, which results in poor cognition

ASTHMA-COPD OVERLAP IS CHARACTERIZED BY THE FACT THAT THE PATIENT HAS FEATURES OF BOTH COPD AND ASTHMA AS A RESULT OF HAVING BEEN EXPOSED TO BOTH ENVIRONMENTAL FACTORS AND THEREFORE THE TWO CANNOT BE SEPARATED



Table 1: Distinctive features of asthma and COPD redirecting towards ACO

Features	Asthma	COPD	ACO
Age of onset	Early onset (usually childhood), however it can commence at any age	>40 years of age	Age ≥40 years, but symptoms may be present in childhood or early adulthood
Pattern of respiratory symptoms	Variable symptoms over time (day to day, or over longer periods), may limit activity. Usually triggered by exercise, emotions including laughter, dust or exposure to allergens	Symptoms are chronic, continuous, particularly during exercise, with 'better' and 'worse' days	Respiratory symptoms such as exertional dyspnea are persistent but variability may be prominent
Lung function	Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR	FEV1 may be improved by therapy, but post-BD FEV1/FVC <0.7 persists	Airflow limitation not completely reversible, but often with current or historical variability
Lung function between symptoms	May be normal	Persistent airflow limitation	Persistent airflow limitation
Past history or family history	Many patients report of allergies and a history of asthma in childhood, and/or family history of asthma	Previous exposure to noxious particles and gases (chiefly tobacco smoking and biomass fuels)	Previously diagnosed asthma, allergies and a family history of asthma, and/or a history of noxious exposures
Time course	There is improvement with treatment, but may result in fixed airflow limitation	Progresses slowly over years despite treatment	Symptoms are partially but significantly reduced by treatment. Progression is usual with high treatment needs
Chest X-ray	Usually normal	Severe hyperinflation and other changes of COPD	Similar to COPD
Exacerbations	Exacerbations occur, but they can be significantly reduced by treatment	Exacerbations can be curtailed by treatment. If present, comorbidities contribute to impairment	Exacerbations are more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment
Typical airway inflammation	Eosinophils and/or neutrophils	Neutrophils in sputum, lymphocytes in airways, may have systemic inflammation	Eosinophils and/or neutrophils in sputum

Abbreviations: ACO, asthma-COPD overlap; AHR, airway hyperresponsiveness; BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Adapted from: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2017. Available at: https://ginasthma.org/wp-content/uploads/2019/04/wmsGINA-2017-main-report-final_V2.pdf. Accessed on 28/05/2019.

and inappropriate management in clinical practice (Table 1).^{2,3}

In 1961, the 'Dutch hypothesis' promulgated that the various forms of airway obstruction, including asthma, chronic bronchitis, and pulmonary emphysema, should be considered as different expressions of one disease entity that occurs as a result of the same genetic factors (atopic status, promotion of airway hyperreactivity), and only

presents different clinical phenotypes owing to different environmental factors, such as allergens, smoking, and infections. In addition, ACO is characterized by the fact that the patient has features of both COPD and asthma as a result of having been exposed to both environmental factors and therefore the two cannot be separated.^{2,4-7}

Conversely, the opposing 'British hypothesis' posited that asthma and COPD are distinct clinical entities engendered

by different mechanisms triggered by different inflammatory cells and mediators. In this hypothesis, it is believed that, in patients with characteristics of both asthma and COPD, both diseases coexist separately in the same individual. The validity of the Dutch and British hypotheses with regard to the mechanism by which features of both asthma and COPD are presented simultaneously are still contentious; therefore, a firm conclusion as to the pathogenesis of ACO remains elusive.^{2,4-7}

PATHOGENESIS OF ACO: PROGRESSION FROM ASTHMA

It is evident that the gradual shift of a patient with either asthma or COPD alone to one with features of both asthma and COPD may necessitate various physiological modifications. Asthma is typically considered a disease of variable airflow obstruction, usually in response to allergen hypersensitivity, whereas the obstruction in COPD is supposed to be incompletely reversible and the outcome of exposure to noxious inhalants, such as cigarette smoke or biomass fuel. It is proposed that patients with asthma who are exposed to the usual inhalants that cause COPD could develop this degree of fixed obstruction over time. Indeed, studies have revealed that individuals with asthma exposed to higher levels of air pollution are at increased risk of developing ACO. Studies conducted among humans with asthma as well as experimental models of asthma reveal that exposures to noxious inhalants lead to neutrophilic inflammation, cytokine release, oxidative stress, DNA methylation changes, and matrix metalloproteinase-mediated proteolysis. These changes may redirect the asthmatic airway to features of COPD, including fixed airways obstruction and emphysema.^{5,8}

IS ACO A PHENOTYPE OF SEVERE ASTHMA?

Asthma-COPD overlap is characterized with persistent airflow limitation and airway inflammation, with the symptoms of frequent and intense cough, wheeze, short of breath and dyspnea. Of note, these clinical manifestations to certain extent resemble the criteria of severe asthma which, according to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines, is defined by the requirement of high-dose ICS and a second controller (or systemic corticosteroids) to prevent asthma from becoming uncontrolled, or the disease remains uncontrolled despite therapy.^{2,9}

Severe asthma, unlike its milder counterpart, is poorly controlled by the standard care. The ERS/ATS consensus defines severe asthma as 'asthma, which requires treatment

PATIENTS WITH ASTHMA-COPD OVERLAP DEFINED BY GUIDELINES AND STUDIES HAVE COMPARABLE CHARACTERISTICS OF SEVERE ASTHMA: EARLIER ONSET WITH WORSE RESPIRATORY SYMPTOMS, MORE EXACERBATION, LOWER SMOKING PACKS, HIGHER RATE OF AIRWAY HYPERRESPONSIVENESS, THICKER AIRWAY WALL AS WELL AS A HIGHER OVERALL RESPIRATORY MORBIDITY, SEEMINGLY SUGGESTING THAT ASTHMA-COPD OVERLAP IS A PHENOTYPE OF SEVERE ASTHMA

with guideline suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier) for the previous year or systemic corticosteroids for more than half of previous year to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy'. The guidelines further elucidated the conditions attributed to uncontrolled asthma, including poor symptom control, frequent severe exacerbation, serious exacerbation, and airflow limitation.^{2,9}

It is interesting to note that the definition of severe asthmatic patients with fixed airflow limitation in the ERS/ATS guidelines is overlapped with that of ACO. As abovementioned, patients with ACO defined by guidelines and studies have comparable characteristics of severe asthma: earlier onset with worse respiratory symptoms, more exacerbation, lower smoking packs, higher rate of AHR, thicker airway wall as well as a higher overall respiratory morbidity. Moreover, ICS-based therapy combined with bronchodilators are generally recommended for both ACO and severe asthma, seemingly reinforcing the notion that ACO is a phenotype of severe asthma (Table 2).^{2,9}

In this context, studies in recent past have demonstrated high clinical similarities between severe asthma and ACO, at least in a proportion of the cohort. To this effect, in an anti-

Table 2: Comparison between ACO and severe asthma

Variables	ACO	Severe asthma
Definition	<p>GINA-GOLD guidelines</p> <p>ACO is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACO is identified in clinical practice by the features that it shares with both asthma and COPD</p>	Asthma which requires treatment with high dose ICS plus a second controller to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy
Diagnostic criteria	<p>GINA-GOLD guidelines</p> <p>A similar number of features of both asthma and COPD, consider the diagnosis of ACO (a stepwise approach to diagnosis is advised for diagnosis of ACO)</p> <p>Spanish ACO guidelines (2 major criteria, or 1 major and 2 minor criteria)</p> <p>Major criteria</p> <ul style="list-style-type: none"> Very positive bronchodilator test (increase in FEV1 ≥15% and ≥400 mL) Eosinophilia in sputum Personal history of asthma <p>Minor criteria</p> <ul style="list-style-type: none"> High levels of total IgE Personal history of atopy Positive bronchodilator test on at least two occasions (increase of FEV1 >12% and >200 mL) 	<p>At least one of the following:</p> <ul style="list-style-type: none"> Poor symptom control: ACQ consistently >1.5, ACT ≤19 Frequent severe exacerbations: 2 or more bursts of systemic CSs (>3 days each) in the previous year Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year Airflow limitation: after appropriate bronchodilator withhold FEV1 <80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal)
Therapy	<p>GINA-GOLD guidelines</p> <p>ICS in a low or moderate dose (depending on level of symptoms); add-on treatment with LABA and/or LAMA. If there are features of asthma, avoid LABA monotherapy</p> <p>Spanish ACO guidelines</p> <ul style="list-style-type: none"> LABA + ICS LAMA + LABA + ICS 	<p>Using established asthma medications</p> <ul style="list-style-type: none"> ICS or OCS SABA or LABA Slow release theophylline LTRA LAMA Specific therapeutic approaches Monoclonal anti-IgE/IL-5/IL-4/IL-13 Methotrexate Macrolide antibiotics Antifungal agents (for ABPA) Bronchial thermoplasty

Abbreviations: ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting β_2 agonist; OCS, oral corticosteroid; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2 agonist; ACQ, asthma control questionnaire; ABPA, allergic bronchopulmonary aspergillosis; ACT, asthma control test.

Adapted from: 1. Xia Y, Cao Y, Xia L, Li W, Shen H. Severe asthma and asthma-COPD overlap: A double agent or identical twins?. *J Thorac Dis*. 2017;9(12):4798–4805. 2. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343–73.

interleukin-4 (IL-4) receptor α monoclonal antibody clinical trial¹⁰ for severe asthma, more than half of the participants expressed persistent airflow limitation, who also met the diagnostic criteria of ACO.^{2,10}

Likewise, in a study by Ghebre and colleagues¹¹ involving 86 severe asthma patients with the average post-FEV₁ predicted of 79.8%, sputum neutrophil count of 63.2% and sputum eosinophil count of 2.1%, 28 patients, subsequent to cluster analysis, were filtered into ACO group; these 28 patients exhibited the average post-FEV₁ predicted of 74.7%, sputum neutrophil count of 70.1% and sputum eosinophil count of 0.7%. These findings suggest that ACO is partly overlapped with severe asthma, particularly the subgroup characterized with persistent airflow limitation and neutrophilic airway inflammation.^{2,11}

In another cohort study,¹² wherein 18,356 young European adults were enrolled and followed up for 9 years, it was observed that patients with ACO shared the identical risk factors, clinical characteristics, including the annual decline of lung function with patients with asthma. However, compared to asthma, patients with ACO had more respiratory symptoms, a higher rate of medication, hospital admission and exacerbations. Findings of this study suggested that at least among young adults aged 20–44 years, ACO syndrome represents a form of severe asthma, characterized by more frequent exacerbations, and it is likely to be the result of early-onset asthma that has progressed to fixed airflow obstruction, possibly because of airway remodeling.

Likewise, a cross-sectional observational study¹³ focusing on patients with moderate-to-severe asthma suggested that the male dominated, profound smoking group with lower lung function was a unique sub-phenotype of asthma, which is consistent with ACO. As evident, the aforesaid datasets, demonstrating considerable clinical similarities between ACO and severe asthma, suggest that ACO might represent a special phenotype of severe asthma.^{2,13}

CONCLUSION

Asthma-COPD overlap is characterized with persistent airflow limitation and airway inflammation, with the symptoms of frequent and intense cough, wheeze, short of breath and dyspnea. Of note, these clinical manifestations to certain extent resemble the criteria of severe asthma. Moreover,

patients with ACO defined by guidelines and studies have comparable characteristics of severe asthma: earlier onset with worse respiratory symptoms, more exacerbation, lower smoking packs, higher rate of AHR, thicker airway wall as well as a higher overall respiratory morbidity. Phenotype-based definitions could barely differentiate ACO from severe asthma; therefore, a cautious speculation, based on available data, could only be made that ACO is a phenotype of severe asthma. Clinical trials with large cohort from different backgrounds and races are warranted to systematically evaluate the clinical, morphological, physiological, cellular and molecular characteristics between severe asthma and ACO both deriving from asthma and COPD.

REFERENCES

1. Woodruff PG, van den Berge M, Boucher RC, et al. American Thoracic Society/National Heart, Lung, and Blood Institute Asthma-Chronic Obstructive Pulmonary Disease Overlap Workshop Report. *Am J Respir Crit Care Med.* 2017;196(3):375–381.
2. Xia Y, Cao Y, Xia L, Li W, Shen H. Severe asthma and asthma-COPD overlap: a double agent or identical twins? *J Thorac Dis.* 2017;9(12):4798–4805.
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2017. Available at: https://ginasthma.org/wp-content/uploads/2019/04/wmsGINA-2017-main-report-final_V2.pdf. Accessed on 28/05/2019.
4. Hikichi M, Hashimoto S, Gon Y. Asthma and COPD overlap pathophysiology of ACO. *Allergology International.* 2018; 67(2):179–186.
5. Leung JM, Sin DD. Asthma-COPD overlap syndrome: pathogenesis, clinical features, and therapeutic targets. *BMJ.* 2017;358:j3772.
6. Kostikas K, Clemens A, Patalano F. The asthma-COPD overlap syndrome: do we really need another syndrome in the already complex matrix of airway disease? *Int J Chron Obstruct Pulmon Dis.* 2016; 11:1297–306.
7. Nakawah MO, Hawkins C, Barbandi F. Asthma, chronic obstructive pulmonary disease (COPD), and the overlap syndrome. *J Am Board Fam Med.* 2013; 26(4):470–7.
8. To T, Zhu J, Larsen K, et al. Progression from Asthma to Chronic Obstructive Pulmonary Disease. Is Air Pollution a Risk Factor? *Am J Respir Crit Care Med.* 2016;194(4):429–38.
9. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J.* 2014;43(2):343–73.
10. Xia Y, Cao C, Li W, et al. Severe asthma and asthma-chronic obstructive pulmonary disease syndrome. *Lancet.* 2016;388(10061):2741–2742.
11. Ghebre MA, Bafadhel M, Desai D, et al. Biological clustering supports both “Dutch” and “British” hypotheses of asthma and chronic obstructive pulmonary disease. *J Allergy Clin Immunol.* 2015;135(1):63–72.
12. de Marco R, Marcon A, Rossi A, et al. Asthma, COPD and overlap syndrome: a longitudinal study in young European adults. *Eur Respir J.* 2015;46(3):671–9.
13. Zeki AA, Louie S. A Sub-Phenotype of Severe Asthma Patients Meet Criteria for Asthma-COPD Overlap Syndrome (ACOS): A Comparative Analysis of Clinical Criteria and Biomarkers. *American Journal of Respiratory and Critical Care Medicine.* 2016;193:A1301.

Administration of sevelamer in a hemodialysis patient with hyperphosphatemia

CASE PRESENTATION

A 54-year-old man presented with 1 year history of hemodialysis (HD) to treat his chronic kidney disease (CKD). His dialysis course was complicated by uncontrolled BP and large interdialytic weight gain while on HD. Despite his disease, he was a workaholic and had a good appetite. His past medical history was significant for acute coronary syndrome 5 years back. He did not have a history of diabetes mellitus or impaired glucose tolerance. His current medications included amlodipine 10 mg BD, ramipril 5 mg BD, and atenolol 25 mg OD, prescribed for his severe hypertension.

CLINICAL EXAMINATION

On examination, the patient's BP was 150/90 mmHg, pulse rate was 76 beats/min and regular, and respiration rate was 20 breaths/min. Physical examination of chest and abdomen showed no abnormalities.

LABORATORY INVESTIGATIONS

- Serum phosphorus - 5.1 mg/dl (elevated)
- Serum calcium - 9 mg/dl (normal)
- Potassium - 3.6 mmol/l (normal)

DIAGNOSIS

Chronic kidney disease-mineral and bone disorder (CKD-MBD).

MANAGEMENT

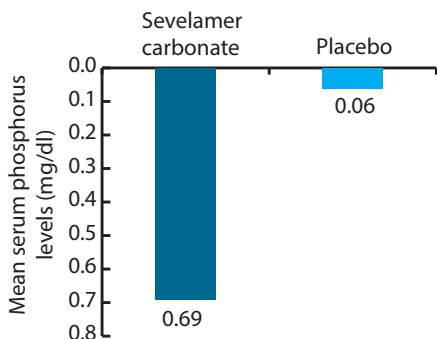
The patient was advised dietary modifications and started with sevelamer carbonate 800 mg thrice a day along with HD. After 1 year, the patient presented for follow-up and his lab tests revealed normal serum phosphorus levels (3.5 mg/dl) and significant improvement in his eGFR.

DISCUSSION

In patients suffering from CKD, with progressive decline of glomerular filtration rate (GFR), the deranged mineral metabolism worsens the bone microstructure and remodelling. This condition is termed as CKD-mineral bone disease (CKD-MBD) and is characterized by – abnormal metabolism of calcium, phosphorus, parathyroid hormone and vitamin D, disturbed bone turnover, mineralization, and soft tissue calcifications (vascular or extra-osseous).¹ The effect of CKD-MBD on phosphorus homeostasis commences in the early stages of the disease and serum phosphate levels are maintained within normal range by hormonal compensations until late CKD, when renal function is so severely deranged that such compensations are not sufficient, leading to hyperphosphatemia.²

Hyperphosphatemia is found to be associated with the development of secondary hyperparathyroidism, reduced serum calcitriol levels, abnormal bone remodeling, and soft-tissue calcification.³ Moreover, hyperphosphatemia is also an independent predictor of cardiovascular disease and mortality in patients with advanced chronic kidney disease (stage 4 and 5).⁴ Apart from the recommendation

Figure 1: Comparative reduction in mean serum phosphorus levels with sevelamer carbonate and placebo



Source: Chen N, Wu X, Ding X, Mei C, Fu P, et al. Sevelamer carbonate lowers serum phosphorus effectively in haemodialysis patients: a randomized, double-blind, placebo-controlled, dose-titration study. *Nephrol Dial Transplant.* 2014;29(1):152-160

to reduce the dietary consumption of phosphorus for management of hyperphosphatemia, phosphate binders are also prescribed to the patients. These act by binding the dietary phosphate within the gastrointestinal lumen to prevent its absorption. These can be calcium-based or calcium-free. Both are almost equally effective, however, there is a risk of hypercalcemia and development of vascular calcifications with the use of calcium based phosphate binders.⁵

Sevelamer carbonate is an improved buffered form of sevelamer hydrochloride. The carbonate anion in sevelamer carbonate provides alkali supplementation that might be beneficial to CKD patients who typically develop metabolic acidosis due to underlying kidney insufficiency and impaired renal hydrogen ion excretion. In a randomized, double-blind, dose-titration study comparing the efficacy of sevelamer carbonate (starting dose 800 mg three times daily) with placebo over 8 weeks in CKD patients on hemodialysis, it was found that the mean serum phosphorus decreased significantly in patients treated with sevelamer carbonate and it was well-tolerated and safe (Figure 1).⁶ Thus, sevelamer carbonate can be an effective therapeutic option for management of hyperphosphatemia in patients with CKD-MBD.

REFERENCES

- Hou YC, Lu CL, Lu KC. Mineral bone disorders in chronic kidney disease. *Nephrology (Carlton).* 2018;23(Suppl 4):88-94.
- Stremke ER, Gallant KMH. Intestinal Phosphorus Absorption in Chronic Kidney Disease. *Nutrients* 2018;10:1364.
- Moschella, Carla PA-C. Chronic kidney disease-mineral and bone disorder: Guidelines for diagnosis, treatment, and management. *JAAPA* 2016;29(7):21-29.
- Chan S, Au K, Francis RS, Mudge DW, Johnson DW, et al. Phosphate binders in patients with chronic kidney disease. *Aust Prescr.* 2017;40(1):10-14.
- Cernaro V, Santoro D, Lacquaniti A, Costantino G, Visconti L, et al. Phosphate binders for the treatment of chronic kidney disease: role of iron oxyhydroxide. *Int J Nephrol Renovasc Dis.* 2016;9:11-9.
- Chen N, Wu X, Ding X, Mei C, Fu P, et al. Sevelamer carbonate lowers serum phosphorus effectively in haemodialysis patients: a randomized, double-blind, placebo-controlled, dose-titration study. *Nephrol Dial Transplant.* 2014;29(1):152-160.

An elderly female with benign paroxysmal positional vertigo managed with high-dose betahistine therapy for 3 months

CASE PRESENTATION AND HISTORY

A 69-year-old woman presented with complaints of persistent dizziness, nausea and occasional vomiting for the past 3 weeks. She was accompanied by her son who noticed her catastrophic symptoms and immediately took her to the hospital.

The patient gave a history of being diagnosed with vertigo about one year ago. At that time, she underwent treatment with cinnarizine 25 mg three times a day as prescribed by her family physician. Initially, she experienced some relief; but similar symptoms resumed soon afterwards. Over the next few weeks, her condition progressively deteriorated despite taking cinnarizine therapy.

At presentation, her condition was complicated by subtle hand tremors, and worrisome vertigo on changing head positions, especially when getting out from the bed. However, she reported no complaints of headache, ear ache and discharge from the ear.

PAST MEDICAL HISTORY

Past medical history revealed that the patient had an episode of fall about 1 year back, which coincided with the time of her diagnosis of vertigo. In addition, she gave a history of hysterectomy done 10 years back for uterine leiomyoma.

PERSONAL AND FAMILY HISTORY

The patient's personal history was negative for alcohol or drug abuse. Family history of the patient was non-contributory.

EXAMINATION

- The patient was conscious and well-oriented to time, place and person; however, she appeared distressed due to the frequent dizziness episodes.
- Her vitals were normal:
 - » Blood pressure (BP): 126/84 mmHg
 - » Pulse rate: 74 beats per minute
 - » Temperature: normal
 - » Respiratory rate: 15 breaths per minute
- General physical examination of the patient was normal, with no signs of cyanosis, icterus or pallor.
- There were no signs of any neurological deficit.

INVESTIGATIONS

- Serum investigations, including hemogram, lipid profile, thyroid function tests and C-reactive protein (CRP), were largely normal.
- She had normal balance and no gross gait deviations.
- Considering her past history of vertigo, vestibular examination was conducted, which revealed absence

of resting nystagmus.

- Neurological examination revealed that cranial nerves II through XII were intact.
- Dix-Hallpike test was normal on the left side, but revealed an upbeat, torsional nystagmus on the right side, which lasted for approximately 30 seconds.
- A head-impulse test was positive; a corrective saccade was noticed on moving the head to the right side.
- Caloric tests were normal.
- Her CT and MRI results were normal.

DIAGNOSIS

The patient was diagnosed with posterior canal benign paroxysmal positional vertigo (PC-BPPV).

MANAGEMENT AND FOLLOW-UP

Cinnarizine was discontinued and the patient was prescribed betahistidine 8 mg twice daily along with ondansetron 4 mg on SOS basis. In addition, Semont maneuver was also advised (Figure 1). Her son was instructed on the technique of the maneuver and she was asked to perform the method at home every night for a week. The treatment resulted in some initial relief, with a subjective decrease in dizziness; however, the vertigo

episodes persisted. She took the medication for about two weeks and then discontinued the treatment.

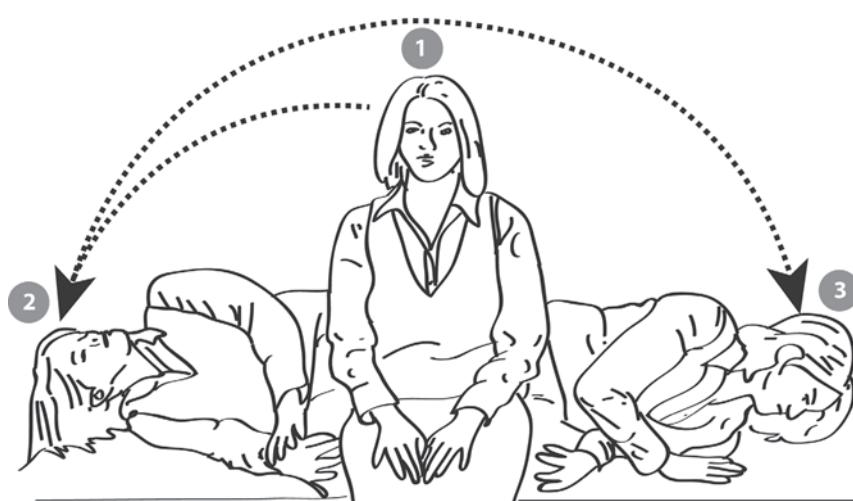
On the follow-up visit, the patient was counseled about the diagnosis and its relapse, and was then started on betahistidine 48 mg/day (administered as 16 mg thrice daily, after meals). The patient complied well with this treatment and presented for follow-up after one month. She reported remarkable improvement in her condition and mentioned that the vertigo episodes were now less frequent with no movement-provoked dizziness. Hence, she was asked to continue the same therapy for a period of another two months after which she reported complete resolution of catastrophic symptoms.

DISCUSSION

Benign paroxysmal positioning vertigo: An overview

Benign paroxysmal positional vertigo is a clinical condition characterized by transient and recurrent episodes of vertigo triggered by changes in head position and movements like looking up, tilting the head back, turning over in bed, or straightening up after bending over.¹ It is reported to be the most common disorder of the peripheral vestibular system with a lifetime

Figure 1: Semont maneuver for posterior canal benign paroxysmal positional vertigo



(1) Initially, the patient is seated in the upright position; then the patient's head is turned 45 degrees toward the left side, and the patient is then rapidly moved to the side-lying position as depicted in position (2). This position is held for approximately 30 seconds, and then the patient is rapidly moved to the opposite side-lying position without pausing in the sitting position and without changing the head position relative to the shoulder, resulting in position (3). This position is maintained for 30 seconds and then the patient gradually resumes the upright sitting position.

Adapted from: Bhattacharyya N, Baugh RF, Orvidas L, et al. Clinical practice guideline: Benign paroxysmal positional vertigo. *Otolaryngology—Head and Neck Surgery*. 2008;139:S47-S81.

prevalence of about 2.4%.^{2,3} There exists a strong female preponderance and a predilection for older age group, particularly the 5th and 6th decades of life.³ BPPV is more likely to involve the right ear, which can be attributed to the habit of sleeping on the right side in most of the people. The condition can affect all three semicircular canals of the ear; however, the posterior canal is involved in 60-90% cases.^{3,4}

Apart from the classical symptoms, patients also report of nonspecific dizziness, postural instability, lightheadedness, nausea, anxiety and sensitivity to all directions of head movement. In addition, BPPV is associated with a characteristic paroxysmal positional nystagmus and its duration correlates well with the vertigo episodes. Observation of these nystagmus patterns help in the diagnosis of BPPV.^{2,4} The Dix-Hallpike maneuver is regarded to be the gold standard for accurate diagnosis of posterior semicircular canal BPPV.²

Vertigo can also present as a symptom in several other otologic conditions like meniere's disease, vestibular neuritis/labyrinthitis, and even in neurologic conditions like migraine and CNS lesions. Furthermore, it may manifest as a side effect of some medications and is also associated with postural hypotension and anxiety.⁵ Therefore, careful history-taking and thorough examination is essential to prevent the misdiagnosis of BPPV and formulate an effective treatment plan.

Management of benign positional paroxysmal vertigo

The treatment modalities include counseling the patient, physical exercises with repositioning maneuvers, and pharmacological agents. Surgical interventions like singular neurectomy and procedures of posterior semicircular canal occlusion are indicated in patients showing poor response to conservative therapy.³ Traditionally, the treatment of BPPV mostly involved restriction of the position change responsible for the episodes of vertigo.⁴ Later, a number of non-invasive techniques such as Semont maneuver and Epley maneuver were developed.^{2,3} Other than repositioning maneuvers, pharmacological therapy is of paramount importance in the management of BPPV.

Appraising the role of betahistine

Betahistine is a histamine analogue which is widely employed in the treatment of vestibular disorders such as BPPV. It is proposed that betahistine may

reduce peripherally the asymmetric functioning of the sensory vestibular organs in addition to increasing vestibulocochlear blood flow by antagonising local H3 receptors.⁶ Several studies have demonstrated betahistine to be effective in reducing the frequency and severity of vertigo along with improving vertigo-associated symptoms such as nausea and vomiting. A placebo-controlled study⁷ was conducted in 24 patients with vertigo of peripheral origin. The subjects were randomized to receive either betahistine dihydrochloride at a dose of 12 mg three times daily or placebo. Results demonstrated that betahistine significantly reduced the incidence of dizziness ($p=0.004$), nausea ($p=0.014$) and vomiting ($p=0.036$) in these patients as compared to placebo, thereby revealing the effectiveness of betahistine in patients with vertigo.

Furthermore, studies also demonstrated that betahistine was well-tolerated in patients with vertigo and it significantly improved quality of life of the patients. These findings were confirmed in a study conducted by Mira *et al*⁸ wherein the efficacy and safety of betahistine dihydrochloride was compared to that of placebo in a group of patients with recurrent vertigo.

Similar results were obtained in another study⁹ conducted in a group of Indian patients with vestibular vertigo. Efficacy was evaluated by administering three patient-reported outcomes (PROs) which assessed dizziness, depression and quality of life outcomes while safety was assessed by recording adverse drug reactions. Results demonstrated significant improvements in self-perceived impairment associated with vertigo along with similar improvement in quality of life outcomes. Furthermore, betahistine was found to be well-tolerated in the study patients with no serious drug-associated adverse effects.

Benefits of longer duration and higher doses of betahistine therapy

It has been suggested that two conditions determine the therapeutic effects of betahistine: dose and duration of therapy.¹⁰ A higher betahistine dose of 48 mg/day for a duration of 3 months is considered to be beneficial in obtaining the maximal effect of the drug in managing vertigo episodes.¹¹ This was evident in a recently conducted multinational study¹² wherein the effectiveness of betahistine was evaluated when administered at a dose of 48 mg/day in a total of 305 patients with vestibular vertigo. The patients were

Table 1: Clinical response of vertigo patients to 2 months betahistidine therapy (48 mg/day) at the end of treatment

Clinical response	Patients with clinical response	
	n	%
Excellent	43	14.1
Very good	79	25.9
Good	104	34.1
Moderate	61	20.0
No change	15	4.9
Worsening	3	1.0

Adapted from: Parfenov VA, Golyk VA, Matsnev EI, et al. Effectiveness of betahistidine (48 mg/day) in patients with vestibular vertigo during routine practice: The VIRTUOSO study. *PLoS One.* 2017;12(3):e0174114.

administered betahistidine for a period of 2 months and further followed up 2 months after treatment discontinuation. Results demonstrated good to excellent clinical response with the regimen in 74.1% patients after 2 months of treatment (Table 1) along with significant reduction in vertigo severity from baseline ($p < 0.001$). In addition, a significant decrease in the monthly vertigo attack frequency during the 2 months of treatment as compared to baseline was reported ($p < 0.001$) along with further reduction during the 2 month follow-up period ($p < 0.001$ from end of treatment). Furthermore, this regimen was found to be well-tolerated with no incidence of major adverse effects.

Thus, betahistidine at a dose of 48 mg/day appears to be effective and well-tolerated in patients with peripheral vestibular disorders like BPPV when administered for a longer duration of time such as 3 months.

CONCLUSION

Benign paroxysmal positional vertigo is a common condition in daily clinical practice. Apart from the classical vertigo symptoms, patients with BPPV also

report of nonspecific dizziness, postural instability, lightheadedness, nausea, anxiety and sensitivity to all directions of head movement. Treatment modalities include counseling the patient, physical exercises with repositioning maneuvers, and pharmacological agents. Betahistidine is a histamine analogue which is widely employed in the treatment of vestibular disorders such as BPPV. Two conditions determine the therapeutic effects of betahistidine: dose and duration of therapy. A higher betahistidine dose of 48 mg/day for duration of 3 months is considered to be beneficial in obtaining the maximal effect of the drug in managing vertigo episodes in vestibular disorders such as BPPV.

REFERENCES

1. Xiang-Dong G. Benign paroxysmal positional vertigo. *J Neurosci Rural Pract.* 2011;2(1):109–110.
2. Parnes LS, Agrawal SK, Atlas J. Diagnosis and management of benign paroxysmal positional vertigo (BPPV). *CMAJ.* 2003;169(7):681–693.
3. Ibekwe TS, Rogers C. Clinical evaluation of posterior canal benign paroxysmal positional vertigo. *Niger Med J.* 2012;53(2):94–101.
4. Lee SH, Kim JS. Benign Paroxysmal Positional Vertigo. *J Clin Neurol.* 2010;6(2):51–63.
5. Nguyen-Huynh AT. Evidence-Based Practice: Management of Vertigo. *Otolaryngol Clin North Am.* 2012;45(5):925–940.
6. Pepa CD, Guidetti G, Eandi M. Betahistidine in the treatment of vertiginous syndromes: a meta-analysis. *Acta Otorhinolaryngol Ital.* 2006;26(4):208–215.
7. Oosterveld WJ. Betahistidine dihydrochloride in the treatment of vertigo of peripheral vestibular origin. A double-blind placebo-controlled study. *J Laryngol Otol.* 1984;98(1):37–41.
8. Mira E, Guidetti G, Ghilardi L, et al. Betahistidine dihydrochloride in the treatment of peripheral vestibular vertigo. *Eur Arch Otorhinolaryngol.* 2003;260(2):73–7.
9. Kirtane MV, Biswas A. Efficacy of Betahistidine by Patient-Reported Outcomes and its Tolerability Profile in Indian Patients with Vestibular Vertigo. *J Assoc Physicians India.* 2017;65(4):18–24.
10. Lacour M. Betahistidine treatment in managing vertigo and improving vestibular compensation: clarification. *J Vestib Res.* 2013;23(3):139–51.
11. Ramos Alcocer R, Ledezma Rodríguez JG, Navas Romero A, et al. Use of betahistidine in the treatment of peripheral vertigo. *Acta Otolaryngol.* 2015;135(12):1205–11.
12. Parfenov VA, Golyk VA, Matsnev EI, et al. Effectiveness of betahistidine (48 mg/day) in patients with vestibular vertigo during routine practice: The VIRTUOSO study. *PLoS One.* 2017;12(3):e0174114.

Challenges and treatment considerations in women with epilepsy: A review

OVERVIEW

Epilepsy is considered to be one of the common neurological disorders in women. Women with epilepsy face specific challenges throughout their life span due to the effects of seizures and antiepileptic drugs on hormonal function, potentially affecting both sexual and reproductive health.¹

Women with epilepsy are considered to be a sub-population distinct from men with a similar diagnosis, particularly due to the distinguishing features. Women have reported several alterations in the frequency and severity of their seizures according to different phases of the reproductive cycle such as puberty, menstrual phases, menopause and pregnancy.²

EPILEPSY IN PREGNANCY: FACTORS DETERIORATING SEIZURE CONTROL

Pregnancy is one of the challenging situations wherein epilepsy may be associated with adverse maternal and fetal outcomes.³ Most women with epilepsy have a normal pregnancy with favorable outcomes; however, there are increased maternal and fetal risks compared to the general population. Potential risk factors that may lead to seizure deterioration need to be taken into consideration (Box 1).⁴

Pregnancy-associated physiological, endocrine, and psychological changes may sometimes alter seizure activity. Furthermore, the unique hormonal surges and metabolic alterations during pregnancy may alter the pharmacokinetics of antiepileptic drugs, which may result in their lower levels and seizure deterioration. Additionally, seizure worsening is considered to be less

in patients who are free of symptoms prior to conception; however, the highest risk is reported with focal epilepsy, use of polytherapy and certain specific antiepileptic drugs.⁵

TREATMENT CHALLENGES: ROLE OF ANTIEPILEPTIC DRUGS IN PREGNANCY

Several challenges are associated with the management of epilepsy in women. These include elevated risk of complications during pregnancy as well as peripartum psychiatric problems as compared to those without epilepsy.¹ Another special challenge is the need to balance teratogenic effects of antiepileptic medications with optimal seizure control.⁶ Exposure to several antiepileptic drugs during pregnancy has been associated with an increased risk of major congenital malformations in the offspring (Table 1).² Thus, choosing an antiepileptic agent which results in optimal seizure control with no teratogenic effects is essential.

Box 1: Factors affecting seizure control during pregnancy and delivery

- Non-compliance with drugs
- Withdrawal of antiepileptic drugs due to fear of teratogenic effects
- Alterations in pharmacokinetics of antiepileptic drugs caused by gestation
- Pregnancy-associated hormonal changes
- Sleep deprivation in pregnancy
- Physical and mental stress in labor

Adapted from: Tomson T, Hiilesmaa V. Epilepsy in pregnancy. *BMJ*. 2007;335(7623):769–773.

Table 1: Major congenital malformations associated with antiepileptic drugs

Antiepileptic drug	Major congenital malformations
Phenytoin	<ul style="list-style-type: none"> Fetal hydantoin syndrome, congenital heart disease, facial clefts
Valproate	<ul style="list-style-type: none"> Neural tube defects, craniofacial disorders, skeletal disorders, cardiovascular diseases, cerebral defects, language problems
Carbamazepine	<ul style="list-style-type: none"> Neural tube defects, congenital heart defects, reduced growth, and hypospadias
Barbiturates	<ul style="list-style-type: none"> Congenital heart defects, craniofacial defects, limb abnormalities, growth deficiency
Benzodiazepines	<ul style="list-style-type: none"> Orofacial clefts
Lamotrigine	<ul style="list-style-type: none"> Non-syndromic facial cleft

Adapted from: Bangar S, Shastri A, El-Sayeh H, Cavanna AE. Women with epilepsy: clinically relevant issues. *Funct Neurol.* 2016;31(3):127–134.

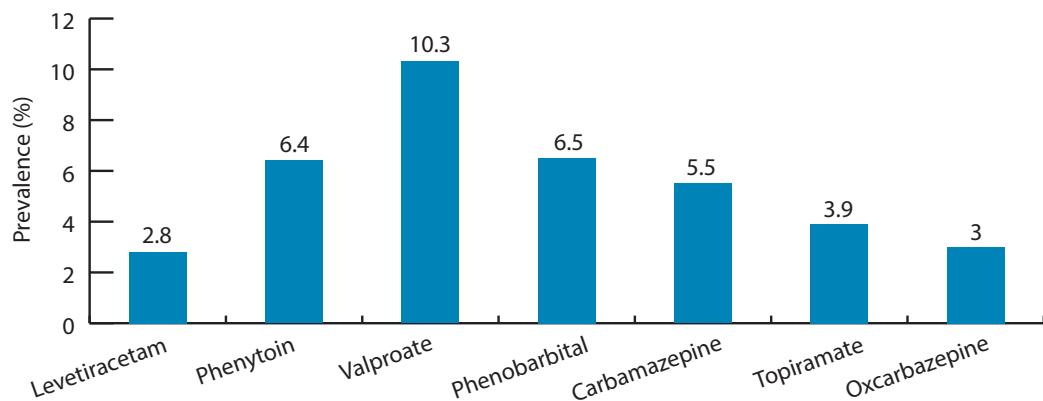
APPRASING THE ROLE OF LEVETIRACETAM IN PREGNANCY

Levetiracetam is an antiepileptic drug that is indicated for the adjunctive treatment of different types of seizures in adults and children.⁷ It is considered to be one of the safest antiepileptic drug in pregnancy in terms of teratogenicity and cognitive outcomes in the child.^{2,8} Due to significantly reduced rates of major congenital malformations with levetiracetam, it may be a preferable option for women in the preconception period.⁹

Several clinical evidences have highlighted the effectiveness and safety of levetiracetam in pregnancy. Studies based on the Spanish EURAP registry¹⁰ and Australian Pregnancy Register¹¹ showed monotherapy with levetiracetam to be as effective as conventional antiepileptic drugs and more efficacious than lamotrigine

and topiramate in controlling seizures during pregnancy. Another recently published prospective cohort study¹² based on the EURAP registry reported lowest prevalence of major congenital malformations with levetiracetam when compared to other commonly used antiepileptic drugs (Figure 1). Similarly, the UK and Ireland Epilepsy and Pregnancy Registry reported a low risk of major congenital malformations associated with levetiracetam monotherapy and suggested it to be a safer alternative to valproate in the management of epilepsy in reproductive-aged women.¹³

Thus, levetiracetam appears to be a favorable antiepileptic drug which effectively controls seizures during pregnancy with low risk of teratogenic effects. Furthermore, it may be a preferred choice of drug in women of reproductive age contemplating pregnancy.

Figure 1: Prevalence of major congenital malformations following use of antiepileptic drugs during pregnancy

Adapted from: Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. *Lancet Neurol.* 2018;17(6):530-538.

REFERENCES

1. Stephen LJ, Harden C, Tomson T, Brodie MJ. Management of epilepsy in women. *Lancet Neurol.* 2019;18(5):481-491.
2. Bangar S, Shastri A, El-Sayeh H, Cavanna AE. Women with epilepsy: clinically relevant issues. *Funct Neurol.* 2016;31(3):127-134.
3. Atarodi-Kashani Z, Kariman N, Ebadi A, Majd HA, Beladi-Moghadam N, Hesami O. Exploring the perception of women with epilepsy about pregnancy concerns: a qualitative study. *Electron Physician.* 2018;10(5):6843-6852.
4. Tomson T, Hiilesmaa V. Epilepsy in pregnancy. *BMJ.* 2007;335(7623):769-773.
5. Treatment of women with epilepsy - Level 1-2: Management and treatment of women with epilepsy during pregnancy. Available at: https://www.ean.org/amsterdam2017/fileadmin/user_upload/TC07_04_Sabers.pdf. Accessed on 12/7/2019.
6. Putta S, Pennell PB. Management of epilepsy during pregnancy: evidence-based strategies. *Future Neurol.* 2015;10(2):161-176.
7. Cormier J, Chu CJ. Safety and efficacy of levetiracetam for the treatment of partial onset seizures in children from one month of age. *Neuropsychiatr Dis Treat.* 2013;9:295-306.
8. Bromley RL, Weston J, Marson AG. Maternal Use of Antiepileptic Agents During Pregnancy and Major Congenital Malformations in Children. *JAMA.* 2017;318(17):1700-1701.
9. Patel SI, Pennell PB. Management of epilepsy during pregnancy: an update. *Ther Adv Neurol Disord.* 2016;9(2):118-129.
10. Martinez Ferri M, Peña Mayor P, Pérez López-Fraile I, et al. Comparative study of antiepileptic drug use during pregnancy over a period of 12 years in Spain. Efficacy of the newer antiepileptic drugs lamotrigine, levetiracetam, and oxcarbazepine. *Neurología.* 2018;33(2):78-84.
11. Vajda FJ, O'Brien T, Lander C, Graham J, Eadie M. The efficacy of the newer antiepileptic drugs in controlling seizures in pregnancy. *Epilepsia.* 2014;55(8):1229-34.
12. Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. *Lancet Neurol.* 2018;17(6):530-538.
13. Mawhinney E, Craig J, Morrow J, et al. Levetiracetam in pregnancy: results from the UK and Ireland epilepsy and pregnancy registers. *Neurology.* 2013;80(4):400-5.

Endothelial effects of sevelamer: Beyond the basics

CARDIOVASCULAR DISEASE IN CHRONIC KIDNEY DISEASE PATIENTS: AN OVERVIEW

Cardiovascular disease (CVD) is the most common cause of mortality for patients suffering from chronic kidney disease (CKD). This condition develops due to multiple pathogenic processes affecting the heart and vessels, such as, atherogenic, inflammatory, and thrombogenic states, endothelial dysfunction, and disrupted blood pressure regulatory molecules.¹

The traditional risk factors for CVD include increasing age, hypertension, dyslipidemia, diabetes, smoking and obesity. These are risk factors for CKD as well and hence are common in patients with CKD. The non-traditional risk factors are ‘uremia specific’, or at least much more common in patients with CKD than in the general population. These include albuminuria, anemia, hyperparathyroidism, metabolic bone disease, hyperhomocysteinemia, malnutrition, apolipoprotein isoforms, etc. The various risk factors tend to have an additive effect and hasten atherosclerosis and progression of CKD and CVD (Figure 1).^{2,3}

VASCULAR ENDOTHELIAL DYSFUNCTION: A KEY ELEMENT FOR CARDIOVASCULAR DISEASE IN CHRONIC KIDNEY DISEASE PATIENTS

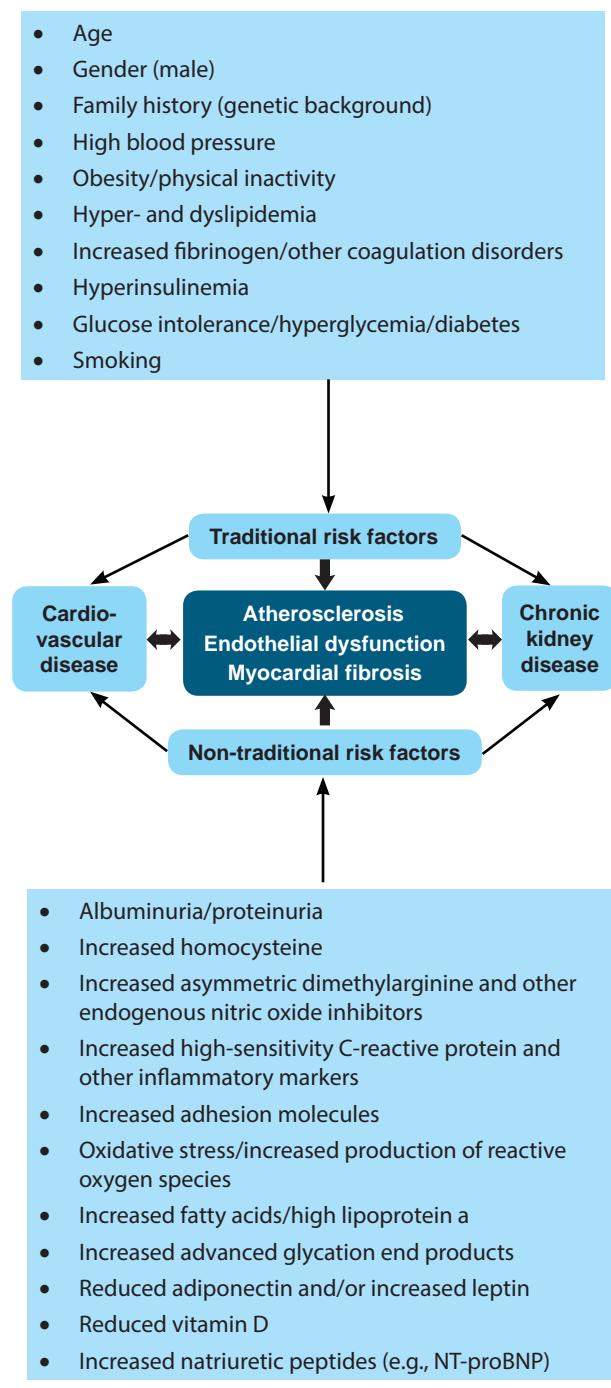
Vascular endothelial dysfunction is being recognized as an important mediator in the development of CVD in CKD patients.⁴ The physiologic effects of the endothelium are primarily vasoprotective, undertaking the suppression of adhesion of leukocytes and monocytes, inhibition of both the migration and proliferation of vascular smooth muscle

cells and platelet aggregation, all of which have a role in the development and progression of atherosclerosis.⁴

The underlying mechanisms of endothelial dysfunction in CKD are multifaceted and appear to evolve throughout the progression of the disease (Figure 2). The early mechanisms possibly involve a reduction in nitric oxide (NO) synthesis and bioavailability.⁵ Nitric oxide (NO) is the most significant and well-characterized vasorelaxant factor produced by the endothelium. It stimulates relaxation of vascular smooth muscle cells and inhibits their proliferation, and prevents leukocyte attachment and migration into the arteries, and platelet adhesion and aggregation to the endothelium.³ In addition, oxidative stress and raised levels of endogenous NOS inhibitor asymmetric dimethylarginine (ADMA) are important contributors. The accumulation of uremic toxins throughout the progression of CKD impairs the transport of L-arginine in the endothelium and this uremic toxin burden eventually becomes so severe that a “uremic switch” occurs in which reduced L-arginine transport becomes the rate limiting step for NO production.⁵

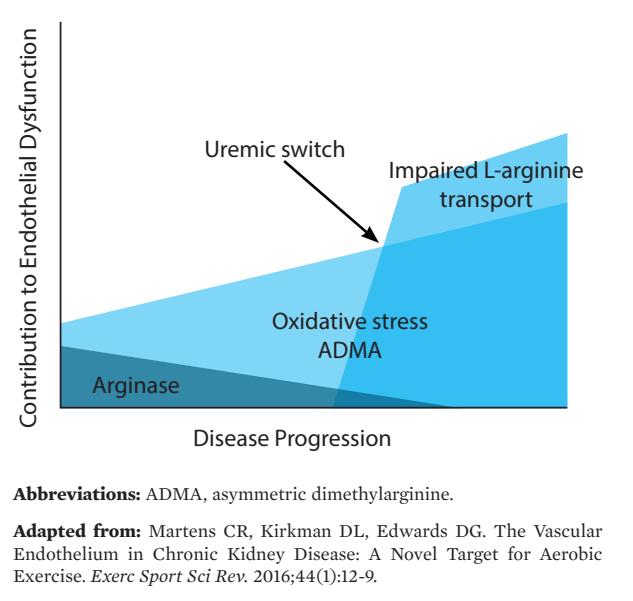
At the same time, endothelial cells also produce several vasoconstrictors, such as endothelin-1, cyclooxygenase-derived prostanoids, reactive oxygen species, dinucleotide uridine adenosine tetraphosphate, and angiotensin II. Whenever an imbalance occurs between endothelium-derived vasorelaxants and vasoconstrictors, endothelial dysfunction follows.³ A dysfunctional endothelium becomes incapable of protecting the vascular system as its antiatherosclerotic and antithrombotic actions get impaired.⁴

Figure 1: Interrelationship between risk factors, cardiovascular disease and chronic kidney disease



Adapted from: 1. Subbiah AK, Chhabra YK, Mahajan S. Cardiovascular disease in patients with chronic kidney disease: a neglected subgroup. *Heart Asia*. 2016;8(2):56–61. 2. Fliser D, Wiecek A, Suleymanlar G, Ortiz A, Massy Z, et al. The dysfunctional endothelium in CKD and in cardiovascular disease: mapping the origin(s) of cardiovascular problems in CKD and of kidney disease in cardiovascular conditions for a research agenda. *Kidney Int Sup*. 2011;1:6–9.

Figure 2: The mechanisms of endothelial dysfunction throughout the progression of chronic kidney disease



Abbreviations: ADMA, asymmetric dimethylarginine.

Adapted from: Martens CR, Kirkman DL, Edwards DG. The Vascular Endothelium in Chronic Kidney Disease: A Novel Target for Aerobic Exercise. *Exerc Sport Sci Rev*. 2016;44(1):12–9.

VASCULAR CALCIFICATIONS: A CONSEQUENCE OF VASCULAR ENDOTHELIAL DYSFUNCTION

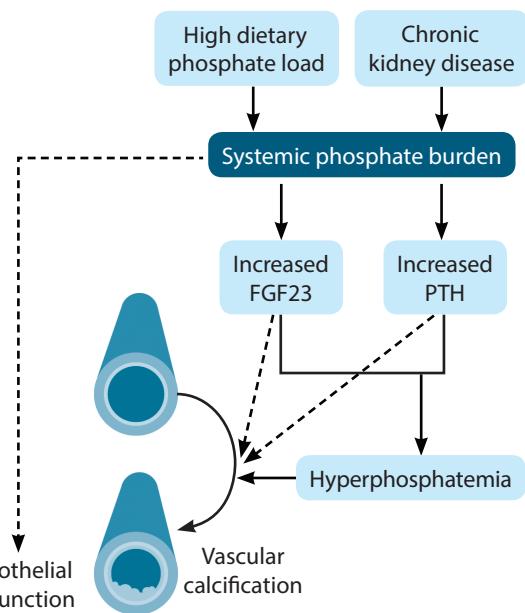
Endothelial integrity plays an important role in the pathogenesis of vascular calcification. It has been demonstrated that secretion of soluble factors by endothelial cells regulates the procalcificant activity in vascular smooth muscle cells (VSMCs).⁶

Moreover, in order to maintain vascular integrity, replacement of damaged endothelial cells with endothelial progenitor cells (EPCs) is done by endothelial microparticles (EMPs). It is speculated that in CKD patients, the endothelial dysfunction causes an increase in circulating EMPs and abnormalities of EPCs, both of which, contribute to the development of vascular calcification in CKD.⁶

ROLE OF PHOSPHATE IN ENDOTHELIAL DYSFUNCTION AND VASCULAR CALCIFICATION

A systemic phosphate burden can be attributed to a high dietary phosphate load or a reduction in the number of functional nephrons (as in CKD). In patients with CKD, an increased production of fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) leads to the development of hyperphosphatemia and consequent vascular alterations (Figure 3).⁷ These alterations include changes in the vessel wall by promoting calcification.

Figure 3: Potential role of phosphate in vascular damage in chronic kidney disease



Abbreviations: FGF23, fibroblast growth factor 23; PTH, parathyroid hormone.

Adapted from: Gross P, Six I, Kamel S, Massy ZA. Vascular Toxicity of Phosphate in Chronic Kidney Disease – Beyond Vascular Calcification. *Circ J*. 2014;78(10):2339-46.

Hyperphosphatemia might also cause vascular dysfunction by stimulating endothelial cells to form microparticles, which then decrease the secretion of annexin II, reduce angiogenesis, increase the production of reactive oxygen species (ROS), enhance inflammation, and result in apoptosis of the endothelial cells.⁸

ENDOTHELIAL EFFECTS OF PHOSPHATE BINDERS: FOCUS ON SEVELAMER CARBONATE

In order to improve clinical outcomes in CKD patients, an important therapeutic target is to decrease the phosphate load and maintain normal levels of serum phosphorus. Strategies to reduce intestinal phosphate absorption include a low-phosphate diet and use of phosphate binders. Phosphate binders are of two main types: calcium-containing and calcium-free binders. Although both the types have similar effects in lowering serum phosphate levels, the calcium-containing binders have been found to contribute to the development and progression of vascular calcification.⁸

Sevelamer carbonate is a calcium-free, intestinally non-absorbed phosphate binder, approved for

hyperphosphatemic dialysis patients in the US and hyperphosphatemic stage 3-5 CKD patients in various other countries. In addition to its primary action of lowering serum phosphate, sevelamer has also been shown to reduce absorption of advanced glycation end products (AGEs), bacterial toxins, and bile acids, indicating its role in reduction of inflammatory, oxidative, and atherogenic stimuli.¹

In a study⁹ conducted by Chennasamudram *et al*, hyperphosphatemic patients on peritoneal dialysis (PD) with Type 2 diabetes mellitus (T2DM) were prescribed sevelamer carbonate or calcium carbonate treatments for eight weeks after a 2-week washout period. The subjects were then crossed over to the other treatment following a second 2-week washout period. It was found that along with the decrease in phosphate levels, sevelamer also had a positive effect on endothelial function in these patients. In another study¹⁰ comparing the effect of sevelamer versus calcium acetate on vascular function in hyperphosphatemic patients with stage 4 CKD, it was found that sevelamer was able to improve endothelial function as evidenced by increase in flow-mediated vasodilatation (6.1% to 7.1%).

Hence, pleiotropic effects of sevelamer may contribute to the improvement of endothelial function in patients with CKD.

REFERENCES

- Rastogi A. Sevelamer revisited: pleiotropic effects on endothelial and cardiovascular risk factors in chronic kidney disease and end-stage renal disease. *Ther Adv Cardiovasc Dis*. 2013;7(6):322-42.
- Subbiah AK, Chhabra YK, Mahajan S. Cardiovascular disease in patients with chronic kidney disease: a neglected subgroup. *Heart Asia*. 2016;8(2):56-61.
- Fliser D, Wiecek A, Suleymanlar G, Ortiz A, Massy Z, *et al*. The dysfunctional endothelium in CKD and in cardiovascular disease: mapping the origin(s) of cardiovascular problems in CKD and of kidney disease in cardiovascular conditions for a research agenda. *Kidney Int Sup*. 2011;1:6-9.
- Perticone F, Maio R, Perticone M, Sciacqua A, Shehaj E, *et al*. Endothelial Dysfunction and Subsequent Decline in Glomerular Filtration Rate in Hypertensive Patients. *Circulation*. 2010;122:379-384.
- Martens CR, Kirkman DL, Edwards DG. The Vascular Endothelium in Chronic Kidney Disease: A Novel Target for Aerobic Exercise. *Exerc Sport Sci Rev*. 2016;44(1):12-9.
- Soriano S, Carmona A, Triviño F, Rodriguez M, Alvarez-Benito M, *et al*. Endothelial damage and vascular calcification in patients with chronic kidney disease. *American Journal of Physiology*. 2014;307(11):F1302-F1311.
- Gross P, Six I, Kamel S, Massy ZA. Vascular Toxicity of Phosphate in Chronic Kidney Disease – Beyond Vascular Calcification. *Circ J*. 2014;78(10):2339-46.
- Lu KC, Wu CC, Yen JF, Liu WC. Vascular Calcification and Renal Bone Disorders. *The Scientific World Journal*. 2014;637065. doi: 10.1155/2014/637065
- Chennasamudram SP, Noor T, Vaslyeva TL. Comparison of sevelamer and calcium carbonate on endothelial function and inflammation in patients on peritoneal dialysis. *J Ren Care*. 2013;39(2):82-9.
- Yilmaz MI, Sonmez A, Saglam M, Yaman H, Kilic S, *et al*. Comparison of Calcium Acetate and Sevelamer on Vascular Function and Fibroblast Growth Factor 23 in CKD Patients: A Randomized Clinical Trial. *Am J Kidney Dis*. 2012;59(2):177-185.

Recent advances in management of neonatal seizures: Levetiracetam as first-line pharmacotherapy

PROLOGUE

Neonatal seizures are one of the most prevalent neurological issues in the newborn period.¹ They are an important example of an age-specific seizure syndrome and the risk of seizures is the highest in neonatal period (3 per 1000 live births).^{2,3} The incidence in pre-term infants is very high (57–132 per 1000 live births). Neonatal seizures predominantly occur in the first week of life.³

The most common cause of symptomatic neonatal seizures is hypoxic/ischemic encephalopathy (HIE). In fact, about two-third cases of neonatal seizures are due to HIE. Other cerebrovascular disorders including arterial and venous stroke, intracerebral hemorrhage and subarachnoid hemorrhage also frequently present clinically with seizures.²

NEONATAL BRAIN: UNIQUELY SUSCEPTIBLE TO SEIZURES

As per recent research, the developing brain is more excitable compared to the mature brain. The enhanced excitability of the developing brain can be attributed to a number of factors including early development of excitatory neurotransmitter systems and delayed development of inhibition.^{1,3} Glutamate is the major excitatory neurotransmitter in the central nervous system that mediates its action via two types of receptors, metabotropic and ionotropic. The ionotropic receptors are further subdivided into N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazol propionic

acid (AMPA), and kainic acid (KA) receptors. During early postnatal development, NMDA and AMPA glutamate receptors are transiently overexpressed as compared to the mature brain and have a subunit composition that enhances excitability.^{1,2}

CLINICAL MANIFESTATIONS OF NEONATAL EPILEPSY

The most widely used scheme for classification of neonatal seizures has been given by Volpe and is solely based on clinical features³.

Subtle seizures: The most frequent neonatal seizures are described as subtle because the clinical manifestations are mild and frequently missed. They are the commonest type and constitute about 50% of all seizures.³ These include tonic, horizontal deviation of the eyes with or without jerking, eyelid blinking or fluttering, sucking, smacking or other oral–buccal–lingual movements, swimming or pedalling movements and, occasionally, apnoeic spells.^{3,4}

Clonic seizures: They are rhythmic movements of muscle groups. They have both fast and slow components, occur with a frequency of 1–3 jerks per second, and are commonly associated with electroencephalogram (EEG) changes.^{3,4} Clonic seizures can be focal, multifocal migrating from limb to limb or, rarely, hemiconvulsive.⁵

Tonic seizures: These seizures manifest as tonic extension of the limbs, mimicking decerebrate or decorticate posturing.^{3,5} The tonic seizures have a

poor prognosis because they frequently accompany intraventricular haemorrhage.³

Myoclonic seizures: Myoclonic seizures are rapid, single or arrhythmic repetitive jerks that may mimic the Moro reflex and startling responses. They may affect the whole body, a finger or limb. They are more frequent in pre-term than full-term infants indicating, massive, major brain injury and poor prognosis. Myoclonic seizures are associated with the most severe brain damage. However, healthy pre-term and rarely full-term neonates may have abundant myoclonic movements. The myoclonic seizures also have a poor prognosis because they are frequently a part of the early myoclonic encephalopathy syndrome.^{3,5}

DIAGNOSTIC INVESTIGATIONS

A comprehensive seizure description and history followed by antenatal history, perinatal history and feeding history must be obtained from the patient. Physical examination should be done and thereafter, the investigations should be performed (Table 1).

MANAGEMENT OPTIONS

Neonatal seizures can be extremely refractory to conventional anti-epileptic drug (AED) treatments, especially those associated with HIE. Seizures due to metabolic or corrective etiologies should be treated by correcting the primary cause.² The drug treatment of neonatal seizures is empirical with significant practice variations amongst clinicians. Phenobarbital and phenytoin are the most commonly used AEDs, although short-acting benzodiazepines are also being used. Large loading doses are followed by a maintenance scheme for a variable period.³

RECENT ADVANCEMENTS IN THE MANAGEMENT OF NEONATAL EPILEPSY

Despite phenobarbital being the gold standard for the management of neonatal seizures for over long time,

there are concerns about its limited effectiveness (given the biology of the newborn brain) and even the tendency to cause neuroapoptosis.⁶ Effective treatment of neonatal seizures has proven challenging with studies suggesting that traditional therapies are only modestly effective. In a study comparing the efficacy of phenobarbital to phenytoin, seizure control was achieved in only about 45% of the patients following administration of the first medication. The patients were then given the alternate medication - increasing seizure control to only about 60%. This study highlighted that 40% of patients continued to have seizures despite treatment with two conventional antiepileptic medications.¹

Acute side effects of phenobarbital and phenytoin include hypotension, respiratory suppression, cardiac arrhythmias, and sedation. Chronic administration of phenobarbital seems to be associated with long-term impairment of neurological development and secondary decrement of cognitive abilities. However, these drugs continue to be administered in the Neonatal Intensive Care Units (NICUs) for the treatment of neonatal epilepsy.⁷

LEVETIRACETAM AS THE FIRST LINE THERAPY FOR TREATMENT OF NEONATAL SEIZURES

Decreased efficacy and adverse neurodevelopmental outcomes of traditional therapies have generated an interest in the use of Levetiracetam (LEV) for the treatment of neonatal seizures.⁸

A study was conducted to evaluate the efficacy and safety of LEV as first-line treatment option for neonatal seizures on 16 neonates with convulsions, admitted in the Neonatal Intensive Care Unit. Intravenous LEV for standard doses was administered and all the patients responded well to the treatment. No patient required a second anticonvulsant therapy and no major side-effects were observed with LEV therapy. This study confirmed

Table 1: Investigations Required in a Neonate with Seizures

Essential investigations (required in all with few exceptional)	Additional investigations
<ul style="list-style-type: none"> Blood sugar Serum Na, calcium, magnesium Cerebrospinal fluid (CSF) examination Cranial ultrasound (US) and Electroencephalography (EEG) and/or amplitude integrated EEG 	<ul style="list-style-type: none"> Hematocrit (if plethoric and/or at risk for polycythemia) Serum bilirubin (if icteric) Arterial blood gas and anion gap (lethargy, vomiting, family history, etc.) Imaging: CT and/or MRI (if no etiology found after essential investigations) TORCH* screen for congenital infections Work-up for inborn errors of metabolism

the efficiency of LEV as first-line treatment option in seizures of this age group.⁷

Another retrospective study evaluated the use of intravenous LEV for acute neonatal seizures, after phenobarbital therapy failure. The study reported that seven of the 22 neonates (32%) had complete seizure cessation by EEG at 1 hour after the loading dose, and 100% had complete cessation at 72 hours, thereby establishing the superiority of Levetiracetam over other drugs for the treatment of neonatal epilepsy. Minimal side effects from Levetiracetam were reported in the study.⁸

As also observed in aforementioned studies, LEV is generally well tolerated by patients. An open label study demonstrated long term tolerance with minimal behavioural and cognitive effects in children 4 to 16 years of age when LEV was used as adjunctive therapy for partial onset seizure.⁸

REFERENCES

- Chapman KE, Raol YH, Brooks-Kayal A. Neonatal seizures: controversies and challenges in translating new therapies from the lab to the isolette. *Eur J Neurosci.* 2012;35(12):1857–1865.
- Jensen FE. Neonatal seizures: an update on mechanisms and management. *ClinPerinatol.* 2009;36(4):881–vii.
- Panayiotopoulos CP. The Epilepsies: Seizures, Syndromes and Management. Oxfordshire (UK): Bladon Medical Publishing; 2005. Chapter 5, Neonatal Seizures and Neonatal Syndromes. Available from: <https://www.ncbi.nlm.nih.gov/books>
- Sankar JM, Agarwal R, Deorari A, Vinod K. Pau Management of Neonatal Seizures *Indian J Pediatr* (2010) 77:1129–1135
- Pressler RM. Neonatal seizures The National Society of Epilepsy. Updated Sept. 2003. Available at <https://www.epilepsysociety.org.uk/sites/default/files/attachments/Chapter06Pressler2015.pdf>. Accessed on May 14, 2019.
- Vesoulis ZA, Mathur AM. Advances in management of neonatal seizures. *Indian J Pediatr.* 2014;81(6):592–598.
- Falsaperla R, Vitaliti G, Mauceri L, et al. Levetiracetam in Neonatal Seizures as First-line Treatment: A Prospective Study. *J Pediatr Neurosci.* 2017;12(1):24–28.
- Mruk AL, Garlitz KL, Leung NR. Levetiracetam in neonatal seizures: a review. *J Pediatr Pharmacol Ther.* 2015;20(2):76–89.

SECTION 3

QUIZ UPDATE



Q1. Which of the following imaging modality is preferred in an acutely ill patient with seizures?

- A. MRI
- B. CT scan
- C. PET
- D. Any of the above

Q2. Valproate is associated with which of the following side-effect(s)?

- A. Postural tremors
- B. Polycystic ovarian syndrome
- C. Thrombocytopenia
- D. All of the above

Q3. Which of these disorders is not a secondary cause of dyslipidemia?

- A. Asthma
- B. Hypothyroidism
- C. Type 2 diabetes
- D. Renal diseases

Q4. Which of these beta-blockers has not shown potential to improve symptoms and reduce hospitalization and mortality rates in heart failure patients?

- A. Carvedilol
- B. Bisoprolol
- C. Metoprolol succinate
- D. Bucindolol

Q5. Which of these is the most appropriate indication for the use of systemic antimicrobials in wound management?

- A. Painful wounds
- B. Large wounds (> 1 cm)
- C. Clinically infected wounds
- D. All wounds

SECTION 4

EVENTS UPDATE

5TH ANNUAL PULMONARY EMBOLISM SYMPOSIUM 2019

October 3-5, 2019
Boston, MA, United States
<https://www.bucme.org/live/7435>

14TH INTERNATIONAL SKELETAL DYSPLASIA SOCIETY MEETING

September 11-14, 2019
Oslo, Norway
<https://www.isds2019.no/>

INDIAN ARTHROSCOPY SOCIETY CONGRESS 2019 (IASCON 2019)

September 27-28, 2019
Indore, India
<http://iascon2019indore.com/>

64TH TRI-STATE CONSECUTIVE CASE CONFERENCE ON LUNG DISEASE

September 13-15, 2019
Ponte Vedra Beach, US/FL, United States
https://action.lung.org/site/TR?fr_id=18275&pg=entry

SECTION 5

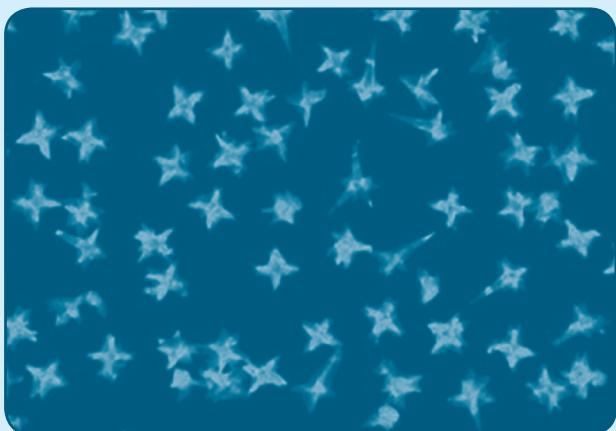
TECH UPDATE

GOLD NANOSTARS HELP DESIGN AND IDENTIFY NEW NANOMEDICINES

Nanomedicine is growing area with vast potential for real-world clinical application in future. Recently, researchers from Northwestern University (NU) presented a novel way to track how nanoparticles interact with the cancer cells. Their work shows that if a nanoparticle targets cancer cells, it undergoes more rotational and translational movement as compared to nanoparticles that cannot effectively target cancer cells. This exciting conceptual development could be of use in screening different nanoparticle formulations based on their physical characteristics (size, charge, shape), and targeting the molecule to see if they effectively target cancer cells *in vitro*. This in sequence could help to develop new more effective nanomedicine cancer therapies.

The researchers chemically synthesized gold nanostars (AuNS), and developed and used a custom microscope to track nanoparticle movements and carefully study how nanostars interact with cancer cells. They found that even though both targeting and non-targeting AuNS had similar proteins binding to their surfaces, they had different interactions with the cancer cells. Non-targeting AuNS did not move very far, and did not have many rotational movements. In contrast, targeting AuNS moved much further around on the cancer cell surface, and underwent many rotations. The technology can be used to identify new nanoparticle formulations to effectively target cancer cells.

Source: <https://www.medgadget.com/2019/08/gold-nanostars-help-design-nanomedicines.html>



FDA APPROVES BAROSTIM NEO NEUROMODULATION DEVICE FOR HEART FAILURE

FDA has recently approved CVRx's first neuromodulation device designed to address heart failure. The device is intended as a treatment option for patients with an ejection fraction (EF) $\leq 35\%$ and New York Heart Failure (NYHF) Classification of III or II (with recent history of Class III), and stimulates the carotid artery and in turn

the baroreceptors that control cardiovascular activity. The system monitors and adjusts the signals it delivers to achieve optimal beat-to-beat stimulation, and could be of use for advanced heart failure patients who are not indicated for Cardiac Resynchronization Therapy (CRT).

FDA's decision was influenced by the results from the Baroreflex Activation Therapy for Heart Failure Pivotal Trial (BEAT-HF), which noted that:

- BAROSTIM NEO is safe for use in patients with heart failure with reduced EF.
- BAROSTIM NEO resulted in clinically significant improvements in patient-centered symptomatic endpoints as compared with the control group.
- The results were supported by objective evidence of significant reduction of NT-proBNP.
- These clinically significant differences in treatment effect were observed regardless of an increase in number of medications in the control arm.

Source: <https://www.medgadget.com/2019/08/barostim-neo-neuromodulation-device-for-heart-failure-wins-fda-approval.html>



VIRTUAL BIOPSY FOR SKIN LESIONS USING VIBRATIONAL OCT

Skin lesions' tissue biopsies can be unpleasant and quite painful, besides the limitation that they typically do not sample the whole lesion and provide limited information about a given lesion's size and depth. Given these limitations, efforts have been underway to develop novel means for effective visualization and analysis of tissue lesions. Recently, scientists at Rutgers University have tested a new device that relies on two different mechanisms to analyze skin lesions. This new "virtual biopsy" device relies on vibrational optical coherence tomography (OCT) to analyze the tissue, and delivers pulses of near-infrared light, along with sound clicks, into the target tissue.

The combination technology can be able to identify how deep a lesion is seated and even whether it looks like it may be malignant. This is because, while the optical component provides information about the size and shape of the lesion, the vibrational component can test its stiffness, a factor that can indicate cancerous nature of the tissue. Since the device does not require skin penetration, there is no pain involved, which is a significant benefit to patients. The virtual biopsy should be beneficial for follow-up interventions, to indicate the shape and depth of a lesion, and therefore provide guidance on surgical decisions. A proof-of-concept study on patients with carcinomas and other lesions has shown that the technology has clinical potential, but more optimization will be required to improve its capabilities for real-world clinical application.

Source: <https://www.medgadget.com/2019/06/virtual-biopsy-for-skin-lesions-using-vibrational-optical-coherence-tomography.html>



SECTION 6

LEGAL UPDATE

Mental health legislation: The Indian scenario

BURDEN OF MENTAL HEALTH ISSUES IN INDIA: AN OVERVIEW

Mental health disorders are considered to be a major concern all over the world, including India. Evidence suggests that about one in every 10 people in the country suffer from mental health issues. Conditions like schizophrenia, bipolar affective disorder, anxiety disorders and alcohol dependence are commonly reported (Figure 1). These disorders are responsible for increased morbidity and the prevalence is more pronounced in males aged 30-49 years. Although the burden of mental illness is high in India, a significantly less proportion

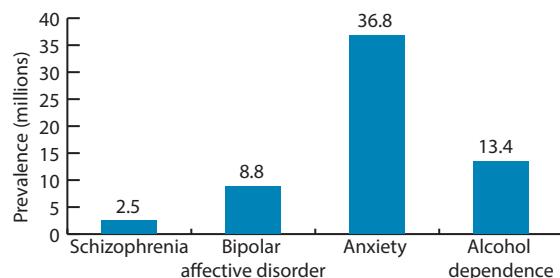
of people have received appropriate treatment.¹ This is mainly attributed to insufficient funding and low mental health awareness. Mental health literacy is an important concept which measures awareness and recognition of mental health disorders. It comprises of various elements which can help in initiating early intervention among individuals (Figure 2).²

MENTAL HEALTH LEGISLATION: LAWS IN INDIA

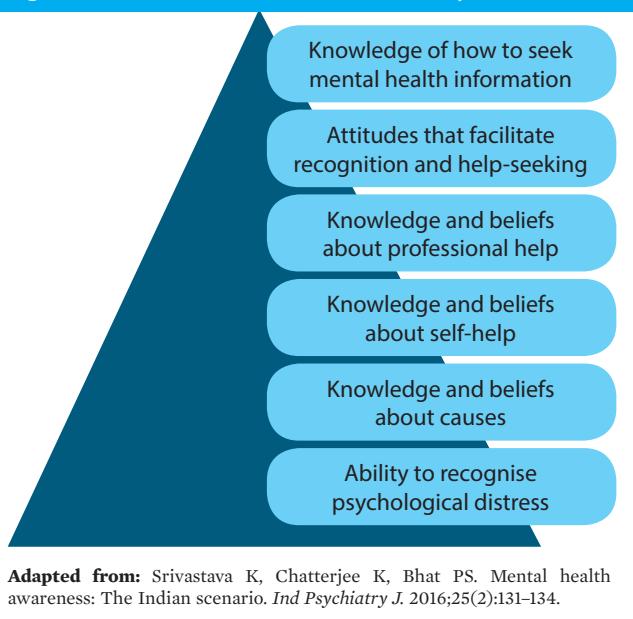
Another important factor that is associated with mental illness and treatment of these disorders is law. As psychiatrists are concerned with diagnosis, treatment



Figure 1: Mental health burden in India



Adapted from: Duffy RM, Kelly BD. Concordance of the Indian Mental Healthcare Act 2017 with the World Health Organization's Checklist on Mental Health Legislation. *Int J Ment Health Syst.* 2017;11:48.

Figure 2: Elements of mental health literacy

Adapted from: Srivastava K, Chatterjee K, Bhat PS. Mental health awareness: The Indian scenario. *Ind Psychiatry J.* 2016;25(2):131-134.

and welfare of patients with mental health disorders, the court and legislation are responsible for mental health issues and its impact on the welfare of the society. Most of the legislations in India in respect of persons with mental disorders have been developed during the British periods. Some of the laws enacted during that time for controlling the care and treatment of patients with mental disorders include the Lunacy (Supreme Courts) Act, the Lunacy (District Courts) Act, the Indian Lunatic Asylum Act and the Military Lunatic Acts. The Indian Lunacy Act was passed in 1912. Following Indian independence, the Indian Psychiatric Society submitted a revised mental healthcare Bill in 1950 which was finally enacted as the Mental Health Act in 1987. The features of this act were as follows:³

- Modern terminology of mental illness and focus on treatment and care rather than custody
- Establishment of central and/or state mental health authority to regulate and monitor the psychiatric hospitals/nursing homes and to advise the government on mental health issues
- Admission in special circumstances in psychiatric hospital/nursing homes
- Establishing the role of police and magistrates to deal with cases of persons with mental illness who were cruelly treated

- Protection of human rights along with guardianship and management of properties of these individuals
- Provisions of penalties in case of breach of provisions of the act.

NEWER LAWS FOR MENTAL HEALTH ISSUES

The Mental Healthcare Bill was passed on 8th of August, 2016 by the Indian Parliament with an aim to provide healthcare and services for persons with mental illness and also to protect, promote and fulfil the rights of such persons while receiving medical management.¹ This has been now adopted as the Indian Mental Healthcare Act (IMHA) which was passed on 7th of April, 2017 and came into force from 7th of July, 2018.^{1,4} This act aims to safeguard the rights of the people with mental illness, along with access to healthcare and treatment without discrimination from the government. It has additionally vouched to tackle the stigma of mental illness, and has outlined measures on how to achieve the same. Hence, the IMHA emerges as a significant step towards increased recognition, enhanced treatment and protection of the rights of the mentally ill in India.¹

CONCLUSION

The burden of mental illness is increasing all over the world, including India. However, a significantly lower proportion of individuals receive appropriate medical treatment for their mental illness due to decreased funding, minimal mental health awareness and the social stigma attached with the issue. Several acts have been passed by the Indian government for providing healthcare services and protecting rights of individuals suffering from mental illnesses. Such acts have emerged as a significant step to promote the wellbeing of those mentally ill in India.

REFERENCES

1. Duffy RM, Kelly BD. Concordance of the Indian Mental Healthcare Act 2017 with the World Health Organization's Checklist on Mental Health Legislation. *Int J Ment Health Syst.* 2017;11:48.
2. Srivastava K, Chatterjee K, Bhat PS. Mental health awareness: The Indian scenario. *Ind Psychiatry J.* 2016;25(2):131-134.
3. Narayan CL, Shikha D. Indian legal system and mental health. *Indian J Psychiatry.* 2013;55(Suppl 2):S177-S181.
4. The Gazette of India. Available at: https://indiacode.nic.in/ViewFileUploaded?path=AC_CEN_12_13_00024_201710_1517807327874/notificationindividualfile/&file=MHA+2017+notification.pdf. Accessed on 23/10/2018.

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OFFICE

UNITED BIOTECH (P) LIMITED

FC/B-1 (Extn.), Mohan Co-operative Industrial Estate, Mathura Road, New Delhi - 110 044

Ph. : +91-11-66611100, 40651100, 66403098/99, 26940762

Fax : +91-11-66607091, 66607096

E-mail : international@unitedbiotechindia.com, ubpl@vsnl.com

Website : www.unitedbiotechindia.com / www.unitedbiotechindia.org