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STANDARD TREATMENT GUIDELINES FOR CHRONIC DISEASES

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ABSTRACT

By the definition of the US national centre for health statistics, a disease persists for a long time that is lasting for three months or more called chronic disease. Chronic diseases generally cannot be prevented by vaccines/cured by medication nor do they just disappear Approximately 25% of the adult population will have hypertension for every 60 seconds a new diabetic is diagnosed, COPD accounts for 4.7 million hospital days per year, schizophrenia quoted as 1% in general population arthritis affects nearly 21 million population of aged and elderly people As the prevalence of chronic diseases is high in worldwide population certain standard treatment guidelines were framed to bringout desired therapeutic outcomes and safety of individuals In this article standard treatment guidelines of hypertension, diabetes mellitus arthritis, Chronic obstructive pulmonary disorder (COPD) and schizophrenia were discussed along with agents, dose, mechanism of action, adverse effects and precautions to be taken during therapy.

KEYWORDS: Chronic diseases, prevalence, standard treatment guidelines, hypertension, diabetes mellitus, arthritis, COPD, schizophrenia.

INTRODUCTION

A disease is a particular abnormal condition that negatively affects the structure or function of part or all of an organism, and that is not due to any external injury.[1,2]

A chronic disease is a human health condition or disease that is persistent or otherwise long lasting in its effect or a disease that comes with time. The term chronic is often applied when the course of disease lasts for more than three months.

Epidemology of Chronic Diseases

The burden of chronic disease is rapidly increasing worldwide .it has been calculated that in 2001 chronic disease contributed approximately 60% of the 565 million total reported deaths and 46% of global burden of disease. The proportion of the burden is expected to increase to 57% by 2020. Approximately 25% of the adult population will have blood pressure of 140/90 mm of hg or higher this may approach 60 million people.[4,5] Diabetes mellitus accounts for 3,00,000 deaths per each year, By every 60 seconds a new diabetic is diagnosed.[6] In US COPD accounts for an estimated 4.7 million hospital days per year with high degree of morbidity.[7,8] In this country alone over 11 million persons has COPD.[9] Morbidity risk of schizophrenia is generally quoted as 1%, but may be as low as 0.4-0.6%.[10,11] Using current diagnostic criteria, one study found 26% of admissions were for mania, 9% for depression, 7% for schizophrenia, and 45% for organic brain disorders, alcoholism, and drug abuse, with 13% undiagnosed.[11] Osteoarthritis affects nearly 21 million middle aged and elderly Americans.[12] Using data from the National Health Interview Survey, it was recently estimated that 14 million people in the US have symptomatic knee OA (KOA), including >3 million racial/ethnic minorities.[13] Rheumatoid arthritis affects between 1 and 2 million Americans, It occurs 3 times more often in women and peaks at age 35 to 5o years.[12] The overall world prevalence of RA is approximately 0.5% to 1%, but may be declining in the United states.[14,15]

Illustration of Standard Treatment Guidelines for Particular Chronic Diseases

S. No.	DISEASE	Standard treatment guidelines
1	Hypertension	Joint national committee on detection evaluation and treatment of high blood pressure -7 report(JNC-7)
2	Diabetes mellitus	American diabetes association (ADA)
3	Arthritis	American college of rheumatology (ARA)
4	Chronic obstructive pulmonary disease	National heart lung and blood institute(NHLBI) World health organization (WHO) The American thoracic society
5	Schizophrenia	American psychiatric association (APA)

Hypertension

Hypertension is an abnormal elevation of arterial blood pressure .In every individual blood pressure varies from minute to minute and is influenced by measurement technique, time of day, emotion, pain, discomfort, hydration, temperature, exercise, posture and drugs.[16] Guidelines on screening for hypertension have been issued by the following organizations:

United States Preventive Services Task Force (USPSTF)

Joint National Committee (JNC)

American College of Obstetriciansand Gynaecologists (ACOG)

Department of Veterans Affairs (VA)/Department of Defence (DoD)

European Society of Hypertension (ESH)/European Society of Cardiology (ESC).[17] It is reasonable to screen for the presence of white coat hypertension using either daytime ABPM or HBPM prior to diagnosis of hypertension.[18]

Stages of Hypertension[12]

Classification	Systolic (mm hg)	Diastolic (mm hg)	Life style modification	Without compelling indication	With compelling indication
Normal pre hypertension	<120 120-139	<80 80-89	yes	No antihypertensive drug indicated, Unless presence of a compelling indication requiring use of drug therapy	Drugs for compelling indication
Stage 1 hypertension	140-159	90-99	Yes	Thiazide diuretics for most, may consider ACE inhibitors, ARB, Beta blockers, CCB or combination	Drugs for compelling indications other antihypertensive drugs diuretics, ACE inhibitors, ARB, Beta blockers, CCB as needed
Stage 2 hypertension	≥ 160	≥100	Yes	2 drug combination for most thiazide type diuretic and ACE inhibitors, ARB, Beta blockers or CCB	Drugs for compelling indications other antihypertensive drugs diuretics, ACE inhibitors, ARB, Beta blockers, CCB as needed

*ACE-Angiotensin converting enzyme

*ARB-Angiotensin receptor blocker

*CCB-Calcium channel blocker

As per JNC-7 (Joint national committee) guidelines the treatment regimen for hypertension:

S. no.	CLASS	AGENT	DOSE(mg)	Mechanism of action	Adverse drug effects	Precautions
1	Thiazide type diuretics	Chlorthalidone Hydrochlorthiazide Indapamide Metolazone	12.5-50 12.5-50 2.5-5.0 2.5- 5.0	Inhibit re absorption of sodium chloride ions from the distal convoluted tubule in kidneys by blocking the	Hypokalemia, increase serum cholesterol, sexual dysfunction,	Electrolyte imbalance, diabetes mellitus, renal impairment

				thiazide sensitive sodium and chloride ions symporter	glucose in tolerance	
2	ACE inhibitors	Captopril Enalapril maleate	50-450 2.5-40	Produce vasodilation by inhibiting the formation of Angiotensin -2	Taste disorder, neutropenia ,proteinuria	Bilateral renal artery stenosis, mitral valve stenosis and collagen vascular disease
3	ARB	Losartan Candesartan Olmesartan Valsartan	50-100 3-8 10-20 80-160	Blocks the action of Angiotensin- 2 preventing to Angiotensin-2	Bronchitis, elevated liver enzymes, headache, dizziness	Renal and mild to moderate hepatic impairment, lactation
4	CCB	Diltiazem Nifedipine Verapamil	120-240 30-120 240-480	Smooth muscle dilators with negative inotropic effect on myocardial atria and ventricles	Flushing, edema, headache, dizziness	Hypertrophic obstructive cardio Myopathy, left ventricular dysfunction
5	Beta blockers	Atenolol Metaprolol Propranolol	50-100 100-450 80-640	Competitive antagonist that block the receptor site for adrenaline and nor adrenaline on adrenergic beta blockers of sympathetic nervous system	Bradycardia, nightmares, decrease high density lipoprotein, increase in triglycerides.	Inadequate cardiac function, broncho spastic disease, diabetes mellitus.

Diabetes Mellitus

ADA (The American Diabetes Association) defines as a group of metabolic diseases characterized by inappropriate Hyperglycemia resulting from defects in insulin secretion,insulin action or both.[12]

It is clear now that diabetes is a heterogeneous group of disorders, almost all of which have a genetic basis, but variation in genetic types.[19]

Classification[12]

Type 1 Diabetes mellitus (T1DM)

It is due to absolute insulin deficiency attributed to an auto immune destruction of beta cells of islets of Langerhans

*Autoantibodies are produced.

TYPE 2 Diabetes mellitus (T2DM)

Identified in individuals age 30 years

*no auto antibodies are produced.

Gestational Diabetes Mellitis (GDM)

Women with first elevated plasma glucose levels during pregnancy.

Other

Secondary diabetes due to other (Cushing syndrome, Acromegaly, cystic fibrosis, down syndrome, pancreatic disorder or treatment for psychotic disorders).

As per ADA guidelines the treatment regimen for diabetes mellitus.

****Types of insulin[12]**

AGENT	Effective Duration(hr)	ONSET(hr)	PEAK(hr)
Rapid acting Lispro(Humalog) Aspart(Novolog) Glulisine(Apidra)	3-4 3-5 3-5	<0.5 <0.5 <o.5	0.5-1.5 0.7-1 0.5-1.5
Short acting regular insulin (Humulin, Novolin regular)	5-8	0.5-1.0	2-4
Intermediate acting NPH (neutral protamine Hagedorn insulin)	10-16	2-4	6-10
Long acting Glargine(Lantos) Detemir(Lavemir)	20-24 12-24	5 3-4	n/a (No applicable) 6-12

Insulin Secretagogues (Oral Hypoglycaemic Agents)[12]

IV	Class	Agent	Dose range	MOA[20]	ADR	Precautions
1	α-glucosidase inhibitors	Acarbose Miglitol	25mg TID	Inhibits intestinal alpha glucosidase slows the digestionof carbohydrates	Diarrhea, abdominal stress	Stress, fever, trauma, infection ,surgeries
2	Biguanides	Metformin	500 mg OD/BD	Activates AMP-kinase and Decrease hepatic glucose production, improves insulin sensitivity	Heart failure, cramping, lactic acidosis,vit B 12 deficiency	CHF,cardiac and respiratory failure
3	Thiazolidinediones	Pioglitazone Rosiglitazone	15-30 MG OD 4 mg OD	Activates the nuclear transcription factor PPAR-gamma and	Wtgain peripheraledema, bone fractures	Mild hepatic impairment, pregnancy and lactation

				increase insulin sensitivity		
4	Sulfonyl ureas	Glipizide Glyburide glimipiride	5mg OD 2-3 mg OD 1-2 mg OD	Insulin release due to closing of ATP sensitive K channels	Hypoglycemia, wt gain	G6PD* deficiency, autonomic neuropathy,thyroid and adrenocortical sinsufficiency
5	Meglitinides	Repaglinide	A_1C*< 8% :0.5 mg A_1C>8%:1 - 2 mg	Bind to SUR* receptors on β cell and release insulin	Hypoglycemia	Myocardial infarction,hepatic and renal impairment
6	Phenylalanine derivatives	Nateglinide	120 mg, TID	Stimulate insulin secretion from pancreas	Hypoglycemia, increased uric acid levels	Adrenal and pituitary impairment
7	DPP-IV inhibitors(dipeptidyl peptidase –IV)	Sitagliptin Saxagliptin linagliptin	100mgOD 2-5mg OD 5mg OD	Inhibit DPP-I V activity and increase in, GLP-1* and GIP conc. Increase in insulin secretion.	Nasopharyngitis, angioedema, utricaria	Hepatic & renal impairment, pregnancy and lactation
8	Bile acid sequestrants	colesevelam	1.875 g BID or 3.75g OD	Bind to bile acid in the gut increase in bile acid production and decrease in hepatic glucose production	Constipation, increased triglycerides	Hepatic impairment,CHF
9	Dopamine agonists	Bromocryptine	0.8mg OD	Modulates hypothalamic regulation of metabolism and increased insulin sensitivity	GI Symptoms, rhinitis,	Risk of conception,peptic ulcer,diabetic retinopathy
10	GLP-1 agonists	Exenatide liraglutide	5mgBID 0.6mg OD	Stimulate glucose dependant insulin release, slows gastric emptying, incresed satiety	Dose related nausea, vomiting, acute pancreatitis	Cardiovascular problems, pancreatitis

11	Amylin agonists	Pramlintide	60mg	Inhibits glucagon secretion and delays gastric emptying, increased satiety	Nausea, vomiting, increase in hypoglycemia	Hepatic and renal impairment

A_1C: Glycated hemoglobin

SUR: sulfonyl ureas

G6PD: glucose 6 phophate dehydrogenase

GLP-1: glucagon like peptide

GIP: glucose dependent insulin tropicpeptide

Osteoarthritis (OA): Osteoarthritis is a common chronic condition of articular cartilage degeneration. Secondary changes can occur in the bone, leading to pain, decreased functioning and even disability.[12]

Treatment Recommendtions[12]

S.NO	CLASS	AGENT	Dose (mg)	MOA	ADE	PRECAUTIONS
1	Analgesic& Antipyretic	Acetaminophen (APAP)	≤4g/dL	Reduces prostaglandins production	Nausea, Allergic reactions, Skin rashes, Acute renal failure, Vertigo	Alcohol dependent, Asthma, Allergic, Monitor Renal and Hepatic impairment,
2	Non-acetylated Salicylates	Salsalate	1000	Inhibition of synthesis & release of prostaglandins	Drowsiness, Ringing in ears, Allergic reactions	Central vascular system
3	Non-Steroid Anti inflammatory drugs	Aspirin Diclofenac Ibuprofen Naproxen	650 75 400 500	Inhibition of enzymes that synthesis prostaglandins	Dizziness, Headache, Necrotising. Gastrointestinal disorders, Stevens Johnson syndrome	Bleeding disorders, increased Bilirubin,
4	Cyclooxygenase 2 inhibitors	Celecoxib	100	Blocks cox-2 Enzymes and decrease the production of prostaglandins	Sinusitis, Upper-restracts of Allergy aggravated, Flatulence, Dysphagia	Ischemic stroke, Dehydration
5	Other Analgesics	Tramadol Codeine	50 15-30	Reduce production of prostaglandins	Dependence, Circulatory failure, Depending	Hypothyroidism, Adrenal Cortical insufficiency, Myasthenia Gravis,

		Capsaicin	0.025-0.075%		Coma, Convulsions, Anorexia	Ultra rapid metabolisers of Codeine
6	Corticosteroids	Prednisone Methyl prednisolone	0.1%	They suppress the immune system, Resulting in decreased in overall inflammation	Weight gain, Head ache, Glaucoma, Obesity	Blurred vision Increased thirst, concentration of urine
7	Hylauronicacid derivatives	Sodium Hyaluronate	20	Water binding ingredients has the ability to fill spaces between connective fibers	Allergic reactions	Pregnancy &lactating women
8	Adjuncts treatment	Glucosamine Chondroitin	500 1200	Stimulate synthesis of synovial fluid, inhibit degradation and improve heeling of articular cartilage	Heart burn, Epigastric pain, Diarrhea, Nausea, Dyspepsia, Constipation, Abdominal pain	Diabetes, pregnancy and lactation

Rheumatoid Arthritis (RA): RA is an autoimmune disease that is usually displayed in the structures of the joints and also having systemic effects like weakness, fatigue, fever and inflammation of other tissues.[21]

Treatment Recommendations.[12]

S. No.	Class	Agent	Dose (mg)	MOA	ADE	Precautions
1	DMARD'S	Methotrexate Sulfasalazine Hydroxychloroquine Minocycline	7.5 500 200 100	Inhibit T&B cells of immune system and suppress inflammatory responses	Nausea, Hepatotoxicity, Rash, Diarrhea, Myopathy, Ocular toxicity	Liver function test, complete blood count, Chest X-ray, Serum creatinine, Hepatitis, B&C
2	Biologicals	Leflunomide Etanercapt Infliximab Adalimumab Anakinra	100 50 3 40 100 mg	Bind to*TNF-α and prevents it action as *TNF produce inflammation& control activity of inflammatory chemicals	Abdominal pain, Diarrhea, Nausea, Dizziness, Rash, Hypertension, Liver toxicity, naso pharyngitis,	Liver function test, Serum creatinine, Complete blood count, Hepatitis B &C, Serology.

		Abatacept Rituximab	10mg 1000mg		arthralgia	
3	Less frequently used DMARDS	Gold salts N-pencillamine Azathiprime cyclosporine	25 mg 125mg 50mg 3mg	Inhibits T & B cells of immune system and suppress.	Proteinuria, chills, leucopenia	Urine analysis, blood pressure

*DMARD'S-Disease modifying anti-Rheumatic drugs

*TNF-Tumor necrosis factor

Chronic Obstructive Pulmonary Diseases

Definition: The national heart, lung and blood institute/WHO, global initiative for chronic obstructive lung disease (GOLD) characterized COPD as "airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of lungs to noxious particles or gases".[12]

The American thoracic society definition is similar: "A disease state characterized by the presence of airflow limitation owing to chronic bronchitis or emphysema. Air flow obstruction is generally progressive may be accompanied by air way hyperactivity and may be partially reversible."

The two major forms of COPD – Chronic bronchitis, Emphysema.[12]

Chronic Bronchitis: It is characterized by production of excessive mucus by the trachea bronchial tree. As a result of edema and bronchial inflammation it results in airways obstruction.

Emphysema: It is characterized by permanent alveolar enlargement distal to the terminal bronchioles.

It causes destructive changes to the alveolar walls.

Treatment for Copd[12]

S NO	CLASS	AGENT	DOSE (mg)	MOA[22]	ADR	PRECAUTIONS
1	Anti cholinergic	Ipratropium bromide Tiotropium bromide atropine	500µg/2.5mL 22.5µg 1.67mg	Block brronchoconstrictor effect of ach on M3 muscarinic receptors in airway smootg muscle	Dry mouth, blurredvision ,constipation, confusion	Prostatic hyperplasia, bladder obstruction ,myasthenia gravis

2	Beta agonists	Salmeterol Formoterol	12mcg 50mcg	Increases mucociliary action by stimulating ciliray activity	Trembling, nervoustension, headche, palpitation	Cardiovascular diseases, CNS disorders
3	Theophylline compounds	Theophylline	5-12µg/mL	Improve ventricular ejection fraction and stimulate renal dieresis	Diarrhea,nausea, vomiting, fast ,muscle tremors	Peptic ulceration, hyperthyroidism, cardiac arrhythmias
4	Long acting selective PDE_4inhibitors (phosphodiesterase 4 inhibitor)	Roflumilast	500 mcg	Shows anti-inflammatory effect and mild bronchodilator effect	Headache,loss of appetite, dizziness, wtloss,abdominal pain	GI problems,
5	1.carticosteroids 2.intravenous Corticosteroids 3.inhaled corticosteroids	Prednisone Prednisolone Methyl prednisolone flovent	40mg 40mg 1-2mg 110µg	Anti inflammatory effect	Osteoporosis, diabetes, wt gain, bruising	Osteoporosis, bacterial pneumonia
6	Antibiotics 1. 2nd generationce phalosporin's 2.β lactamase inhibitors 3.macrolides 4.oral Fluoroquinolone	Cefuroxime, Cefaclor Amoxicillin, Amoxicillin Clavulanate, Azithromycin Ciprofloxacin levofloxacin	250-500 mg 250-500mg 3mg 500 500-750mg 500mg	Treat exacerbation with suspected infection	Bloating, indigestion, diarrhea, vomiting,loss of appetite	Hypersensitivity, renal impairment, pregnancy and lactation,fatal heart arrhythmiasis, epilepsy
7	Mucolytics	Oral N-Acetyl cysteine	600mg	Improve sputum clearance and disrupt mucus plugs	Inflammation of themouth, runny nose,fever, chest tightness	Peptic ulcer diseases
8	Expectorants	Guanifenesin	600-2400mg	Increase the volume and reduce the viscosity of secretions in trachea and bronchi	Dizziness, drowsiness, decreased uric acid levels ,rashes,	Fever, continuous cough
9	Anti oxidants	N acetyl cysteine	1200mg	Reduces the disulfide bonds in the mucous matrix and lowers mucous viscosity	Runny nose, inflammation of mouth, nausea, vomiting, fever	Peptic ulcer disease, bronchospasm

Schizophrenia: It is a major psychiatric disorder affecting approximately 1-2% world population. It includes symptoms like hallucinations, delusions decreased affect, disorganized speech and behavior, impaired functioning.[12]

Types of Schizophrenia[10]

Five types of schizophrenic disorders are recognized by American Psychiatric Association's Diagnostic and Statistical Manual (DSM-III).

1. Catatonic Schizophreia: motor symptoms are seen, bizarre voluntary movements.

2. Disorganised Schizophrenia: flat effect, bizarre mannerisms, grimacing

3. Paranoid Schizophrenia: Most common type paranoid delusions/auditory hallucinations.

4. Residual Schizophrenia: flat effect, social withdrawal, loose associations.

5. Un Differentiated Schizophrenia: The patient meets the criteria for a diagnosis of schizophrenia.

Pharmacotherapy Of Schizophrenia:[12] Anti psychotic medications

Current American psychiatric association (APA) guidelines recommended

Response to medication is not immediate and maximal treatment response may take 6 months or longer to be seen.

After a treatment response is seen patient should maintain current therapy for minimum 6 months.

Major will require chronic therapy because 80% of first episode patient who donot receive anti psychotictreatment will relapse within 5years1.[12]

Anti psychotics are of 2 types as follows.[12]

Typical antipsychotics	Atypical antipsychotics
Chlorpromazine	
Trifluoperazine	Clozapine
Thioridazine	Risperiodone
Perphenazine	Olanzapine
Fluphenazine	Quetiapine
Thiothixene	Ziprasidone
Haloperidol	Aripiprazole
Molindone	Paliperidone
loxapine	

Typical Antipsychotics[12]

S. NO.	AGENT	DOSE(mg/day)	MOA	ADE	Precautions
1	Chlorpromazine	300-1000		Involuntary movement of extremities also occur	Parkinson's disease, Myasthenia Gravis, Avoid direct sunlight
2	Thifloroperazine	5-15	Block Dopamine TYPE-2 (D_2)	Amenorrhea, blood dyscrasis, dry mouth,	Benign prostatic impairment, Hyperplasia,

			receptors. Agent in this class vary in their Activity at Histamine, Muscuranic and &α receptors	blurred vision	angle –closer Glaucoma, Epilepsy
3	Thioridazine	300-800		Polymorphic ventricular, Tachycardia	Cardio disease, Narrow-angle glaucoma, Dementia related psychosis
4	Perphenazine	16-64		Muscle spasm, Blurred vision, Constipation	Breast cancer, Parkinsonism, Lung infection, Inflammatory bowel disease
5	Fluphenazine	5-20		Tardive dyskinesia, sedation, Mental confusion	Elevate prolactin levels, Exacerbation depression, Convulsion disorder
6	Thiothixene	15-50		Tremors, Uncontrolled muscle movement of face	Allergies, Heart problem, Liver disease, Parkinsonism, Seizures
7	Haloperidol	5-20		Tardive dyskinesia, Extra pyramidal reactions, Anorexia	Anticoagulant, Parkinsonism, Epilepsy, prostatic hyperplasia, Allergy
8	Loxapine	5-20		Arrhythmia, Blood pressure, Orthostatic hypotension	Pneumonia, Breast cancer Cardio disease
9	Molindone	30-100		Akathisia, Extra pyramidal symptoms, Dystonia	Galactorrhea, Intestinal obstruction, Leucopenia, Mental retardation, Brain tumor.

Atypical Antipsychotics[12]

S. NO	AGENT	DOSE (mg/day)	MOA	ADR	PRECAUTIONS
1	Clozapine	150-600	Dopamine antagonists but also potentiallyblock 5-HT_{2A}-receptors	Sedation, weight, Reversible neutropenia, Eosinophilia, Tachycardia.	Stroke history for long QT syndrome, Seizures and conditions that lowers the seizures threshold.
2	Risperidone	2-8		Agitation, Anxiety, Tardive dyskinesia,	Pre existing cardio vascular disease, Epilepsy, Tardive dyskinesia.
3	Olanzapine	10-30		Exacerbation of pre-existing diabetes, Agranulocytosis	Cardio vascular disease, conditions with pre disposing hypotension.
4	Quetiapine	300-800		Angioedema, Neuroleptic malignant syndrome	Dementia, related psychosis, Hypotension
5	Ziprasidone	120-200		Weight gain, Runny nose, Hypotension, Headache, Cough	Allergies, pediatrics, Geriatrics, Breast feeding.
6	Aripiprazole	10-30		Neutropenia, Thrombocytopenia, Pathological gambling, Neuroleptic malignant syndrome	Dementia related psychosis, Head trauma, cardio vascular disease
7	Paliperidone	3-12		Tachycardia, Dizziness,	Lightheadedness, Fainting.

In 2005, the Indian Psychiatric Society came up with treatment guidelines for schizophrenia tailored to meet the requirements of our patients in the context of prevailing existing resources.

Antipsychotic Depot Preparations Available In India.[23]

Name of Antipsychotic	Usual 2-4 Weekly Dose (MG)
Zuclopenthixol decanoate	200
Paliperidone palmitate	234 initially followed by 117
Fluphenazine decanoate	12.5-50
Haloperidol decanoate	50
Risperidone depot	25-50
Olanzapine pamoate	210-405

CONCLUSION

From this review, we focus on standard treatment guidelines which play a major role in treating chronic disease for maximum extent, helpful to improve quality of life and improves

socio-economic status of patient.Outcome may be improved with quality improvement strategies at the health system, provider and patient level.

CONFLICTS OF INTEREST STATEMENT

None of the authors have conflicts of interest with respect to this work.

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