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the SQUARE Healthcare bulletin

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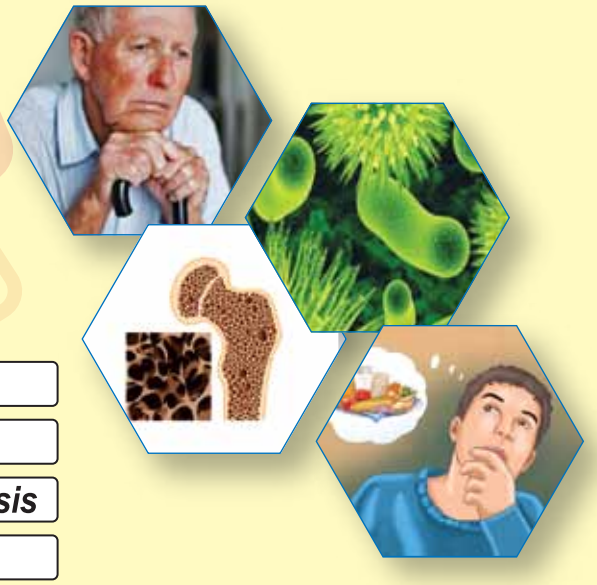

- Parkinson's Disease
- Superbug Manifestation
- Postmenopausal Osteoporosis
- Type 1 Diabetes in Children

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the SQUARE
healthcare bulletin

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Editorial

Dear Doctor,

Welcome to this addition of *"the SQUARE"* healthcare bulletin!

As this is the introductory issue of 2017, we take this opportunity to offer our best wishes from the editorial team of *"the SQUARE"* ! We present this bulletin in a new look!

This edition encompasses a blend of topics. Firstly, we bring out the continuance of a chronic, progressive neurological disorder, the "Parkinson's Disease" (the first part was published in our previous issue of this healthcare bulletin). In this segment the "Treatment of manifestations" of this disorder is vividly highlighted. We have presented a feature on "Superbug Manifestation". These superbugs multiply rapidly creating dangerous outbreaks in the hospitals and cities, and are very difficult to kill with conventional antibiotics or drugs. The bug has at this moment the potential to make all the present antibiotics redundant. A topic on "Postmenopausal Osteoporosis", a widespread, debilitating disease has been incorporated in this issue. The personal and economic burden of postmenopausal osteoporosis results from osteoporotic fractures, are a significant public health problem, resulting in substantial morbidity and mortality. Postmenopausal osteoporosis is also likely to become more common in the decades ahead as the life expectancy of the population increases. We also bring you the details on "Type 1 Diabetes in Children" that showed a worldwide increase towards the end of the 20th century. Our regular feature "Test Yourself" is also included in this issue as well.

We believe that you will find this issue appealing and enlightening!

On behalf of the management of *SQUARE,* we wish you all healthy, prosperous and long lives!

Thank you!

Omar Akramur Rab

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Key title: The square (Dhaka)
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The goal of medical management of Parkinson's disease is to provide control of signs and symptoms for as long as possible while minimizing adverse effects. Studies demonstrate that a patient's quality of life deteriorates quickly if treatment is not instituted at or shortly after diagnosis.

Symptomatic and neuroprotective therapy

Pharmacologic treatment of Parkinson's disease can be divided into symptomatic and neuroprotective (disease modifying) therapy. At this time, there is no proven neuroprotective or disease-modifying therapy.

Symptomatic Therapy, Early Disease

Medications commonly used for symptomatic benefit of motor symptoms in early Parkinson's disease include levodopa, monoamine oxidase (MAO)-B inhibitors and dopamine agonists.

Levodopa

Levodopa, coupled with a peripheral dopa decarboxylase inhibitor such as carbidopa, remains the standard of symptomatic treatment for Parkinson's disease. It provides the greatest antiParkinson'sian benefit with the fewest adverse effects in the short term. However, long-term use of levodopa is associated with the development of fluctuations and dyskinesias.

Once fluctuations and dyskinesias become problematic, they are difficult to resolve. Levodopa/carbidopa is also available in combination with entacapone, a catechol-O-methyltransferase (COMT) inhibitor. Levodopa/carbidopa/entacapone is useful in advanced Parkinson's disease in patients with motor fluctuations but not with early Parkinson's disease.

MAO-B inhibitors

MAO-B inhibitors, such as selegiline and rasagiline, may be used for early symptomatic treatment of Parkinson's disease. These medications provide mild symptomatic benefit, have excellent adverse effect profiles and may improve long-term outcomes. These characteristics make MAO-B inhibitors a good choice as initial treatment for many patients.

Dopamine agonists

Initial treatment with a dopamine agonist, to which levodopa can be added as necessary, is associated with fewer motor fluctuations and dyskinesias than levodopa alone. The benefit of dopamine agonists in delaying motor symptoms is due to their ability to delay the need for levodopa/carbidopa. Commonly used dopamine agonists include pramipexole and ropinirole.

Dopamine agonists provide symptomatic benefit that is comparable to that with levodopa/carbidopa in early disease, but these agents lack sufficient efficacy to control signs and symptoms by themselves in more advanced disease.

Dopamine agonists are commonly reserved for younger individuals (< 65-70 years) who are cognitively intact.

For patients aged 65-70 years, the physician should make a judgment based on general health and cognitive status.

Anticholinergic agents

Anticholinergic agents can be used for patients who have disability due to tremor that is not adequately controlled with dopaminergic medication, but these are not first-line drugs, because of their limited efficacy and the possibility of neuropsychiatric side effects. Because tremor may respond to one anticholinergic medication but not another, a second anticholinergic agent usually can be tried if the first is not successful.

One of the most commonly used anticholinergic is trihexyphenidyl. Benztropine is also commonly used. Amantadine is an antiviral agent that has antiparkinsonian activity. Its mechanism of action is unknown, but amantadine appears to potentiate CNS dopaminergic responses.

Symptomatic Therapy, Advanced Disease

Motor fluctuations

Patients initially experience stable, sustained benefit through the day in response to levodopa. However, after several months to years, many patients notice that the benefit from immediate-release (IR) levodopa/carbidopa wears off after 4-5 hours. Over time, this shortened duration of response becomes more fleeting. Ultimately, benefit lasts only about 2 hours. The time when medication is providing benefit for bradykinesia, rigidity and tremor is called "on" time, and the time when medication is not providing benefit is called "off" time.

Treating motor fluctuations in the absence of peak-dose dyskinesia is relatively easy. Several different strategies can be used to provide more sustained dopaminergic therapy, such as:

- Adding a dopamine agonist, catechol-O-methyltransferase (COMT) inhibitor or monoamine oxidase (MAO)-B inhibitor
- Dosing levodopa more frequently
- Increasing the levodopa dose
- Switching from immediate-release (IR) to sustained-release (CR) levodopa/carbidopa or levodopa/carbidopa/entacapone
- Continuous intrajejunal infusion of a carbidopa/levodopa enteral suspension

Dyskinesia

By several months to years after the introduction of levodopa, many patients develop peak-dose dyskinesia consisting of choreiform, which is twisting/turning movements that occur when levodopa-derived dopamine levels are peaking. At this point, increasing dopamine stimulation is likely to worsen peak-dose dyskinesias, and decreasing dopamine stimulation may worsen Parkinson's disease motor signs and increase off time. The therapeutic window lies above the threshold required to improve symptoms (on threshold) and below the threshold for peak-dose dyskinesia (dyskinesia threshold). The therapeutic window narrows over time because of a progressive decrease in the threshold for peak-dose dyskinesia.

Treatment of motor fluctuations with dyskinesia

The treatment of patients with both motor fluctuations and troublesome peak-dose dyskinesia can be difficult. The goal of treatment in this situation is to provide as much good functional time through the day as possible. This is accomplished by maximizing on time without troublesome dyskinesia. An attempt is made to reduce both off time and time with troublesome or disabling dyskinesia. Unfortunately, a decrease in dopaminergic therapy may increase off time and an increase in dopaminergic therapy may worsen peak-dose dyskinesia.

For patients who have motor fluctuations and dyskinesia that cannot be adequately managed with medication manipulation, surgery is considered.

Tremor

Levodopa/carbidopa, dopamine agonists and anticholinergics each provide good benefit for tremor in approximately 50-60% of patients. If a patient is experiencing troublesome tremor and if symptoms are not controlled adequately with one medication, another should be tried. If the tremor is not controlled adequately with medication, surgical therapy may be considered at any time during the disease.

Nonmotor symptoms

Recognition of nonmotor symptoms of Parkinson's disease is essential. Nonmotor symptoms can be categorized as autonomic, cognitive/psychiatric and sensory and may include depression, dementia, hallucinations, rapid eye movement (REM) sleep behavior disorder (RMD), orthostatic hypotension and constipation. It is important to screen Parkinson's disease patients for depression and treat it when present.

In 2010, the American Academy of Neurology (AAN) released guidelines on the treatment of nonmotor symptoms of Parkinson's disease. Recommendations included the following:

- Sildenafil for erectile dysfunction
- Polyethylene glycol for constipation
- Modafinil for patients who subjectively experience excessive daytime somnolence
- For insomnia, evidence is insufficient to support or refute the use of levodopa or melatonin
- Levodopa/carbidopa for periodic limb movements of sleep, insufficient data of nonergot dopamine agonists
- Methylphenidate for fatigue
- Evidence is insufficient for specific treatments of orthostatic hypotension, urinary incontinence, anxiety and RMD

Putative Neuroprotective Therapy

Neuroprotective therapies are defined as those that slow underlying loss of neurons. Currently, no proven neuroprotective therapies exist for Parkinson's disease. At present, the greatest interest in possible neuroprotection resides with the monoamine oxidase (MAO)-B inhibitors, selegiline and rasagiline. Other agents of interest include creatine and isradipine. Clinical trials have not provided support for neuroprotective effects for vitamin E or coenzyme Q10.

Deep Brain Stimulation (DBS)

Deep brain stimulation (DBS) has become the surgical procedure of choice for Parkinson's disease for the following reasons:

- ❏ It does not involve destruction of brain tissue
- ❏ It is reversible
- ❏ It can be adjusted as the disease progresses or adverse events occur
- ❏ Bilateral procedures can be performed without a significant increase in adverse events

Continued refinement of the knowledge of basal ganglia circuitry and Parkinson's disease pathophysiology has narrowed the focus of movement disorder surgery to 3 key gray-matter structures: the thalamus, the globus pallidus and the subthalamic nucleus (STN).

Thalamic DBS is now rarely used but recent landmark studies have demonstrated the effectiveness of STN and GPi DBS.

The UK National Collaborating Centre for Chronic Conditions notes the following indications for STN and GPi in patients with Parkinson's disease:

- ❏ The presence of motor complications refractory to medical therapy
- ❏ The absence of significant comorbidities in a biologically fit individual
- ❏ The absence of significant mental health problems (eg, depression, dementia)
- ❏ Response to levodopa

A key to patient selection is that appropriate patients still experience a good response to levodopa, but that response cannot be adequately maintained through the day or is complicated by excessive dyskinesia.

STN DBS may be effective in improving specific types of pain related to Parkinson's disease, such as musculoskeletal pain and dystonic pain.

Neuroablative Lesion Surgeries

Lesion surgeries involve the destruction of targeted areas of the brain to control the symptoms of Parkinson's disease. Lesion surgeries for Parkinson's disease have largely been replaced by deep brain stimulation (DBS). During neuroablation, a specific deep brain target is destroyed by thermocoagulation.

Thalamotomy and pallidotomy

Thalamotomy involves destruction of a part of the thalamus, generally the ventralis intermedius (VIM), to relieve tremor. The VIM nucleus is considered the best target for tremor suppression, with excellent short- and long-term tremor suppression in 80-90% of patients with Parkinson's disease. Thalamotomy has little effect on bradykinesia, rigidity, motor fluctus pallidus interna (GPi) and subthalamic nucleus (STN), are preferred.

Pallidotomy involves destruction of a part of the GPi. Pallidotomy studies have demonstrated significant improvements in each of the cardinal symptoms of Parkinson disease (tremor, rigidity, bradykinesia), as well as a significant reduction in dyskinesia.

Subthalamotomy

Subthalamotomy involves destruction of a part of the STN. Although it usually has been avoided because of the concern about producing hemiballismus, results obtained by experimental lesions of the STN in animals and humans suggest that subthalamotomy may be performed safely and may reverse parkinsonism dramatically. Subthalamotomy studies have shown significant improvements in the cardinal features of Parkinson disease, as well as the reduction of motor fluctuations and dyskinesia.

Preoperative Evaluation

Good surgical outcomes begin with careful patient selection and end with attentive, detail-oriented postoperative care. This level of care is best provided by a multidisciplinary team that includes a movement disorder neurologist, a neurosurgeon who is well-versed in stereotactic technique, a neurophysiologist, a psychiatrist and a neuropsychologist. Additional support from neuroradiology and rehabilitation medicine is essential.

First, a neurologist with expertise in movement disorders evaluates the patient. Patient selection is particularly important for successful subthalamic nucleus (STN) deep brain stimulation (DBS), because a number of factors determine positive surgical outcome. Potential surgical candidates are then evaluated by the neurosurgeon, who determines whether the patient is indeed a surgical candidate and decides which procedure(s) would benefit the patient most.

Close collaboration between the neurologist and the neurosurgeon aids the decision-making process, minimizing patient confusion and stress. If the neurologist and neurosurgeon agree that the patient is a good surgical candidate, further workup includes the following:

- Brain magnetic resonance imaging (MRI) to rule out comorbid conditions and to assess the degree of brain atrophy; significant atrophy may increase the risk of perioperative hemorrhage
- Detailed neuropsychological testing to rule out cognitive impairment, which can be worsened by the surgical procedure

A psychiatrist with expertise in psychiatric complications of movement disorders may be consulted to rule out active psychiatric disease and screen for relevant past psychiatric history that may pose a contraindication to surgery (eg, major depression, suicidality). A fluorodopa positron emission tomography (PET) scan may be performed in the unusual circumstance of diagnostic uncertainty. A medical evaluation is performed to determine the patient's general fitness for surgery.

Surgery is reserved for patients with disabling motor fluctuations and dyskinesia or disabling tremor that cannot be adequately controlled with medications. Before surgery, the patient should be informed that these procedures do not cure Parkinson's disease and that progression is expected.

Neural Transplantation

Neural transplantation is a potential treatment for Parkinson's disease, because the most significant neuronal degeneration is site and type specific (ie, dopaminergic); the target area is well defined (ie, striatum); postsynaptic receptors are relatively intact; and the neurons provide tonic stimulation of the receptors and appear to serve a modulatory function.

Gene Therapy

Several studies have demonstrated the safety of gene therapy as a treatment for Parkinson's disease, and larger studies have been initiated to examine the efficacy of this procedure. Three investigational strategies that use gene transfer for targeted protein expression are as follows:

- Improving dopamine availability to the striatum using more continuous delivery,
- Reducing STN activity with local induction of gamma-aminobutryic acid (GABA) expression
- Protection/restoration of nigrostriatal neuronal function with trophic factor expression

Management of Psychiatric Comorbidities

Dementia

Although no specific therapy exists for dementia, the American Academy of Neurology evaluated the evidence regarding the use of cholinesterase inhibitors in Parkinson's disease dementia. Based on their review, they suggested that rivastigmine and donepezil are probably effective in treating Parkinson's disease dementia. Anticholinergic drugs used for the treatment of motor symptoms of Parkinson's disease may exacerbate memory impairment. When possible, avoid these medications.

Depression

Depression is one of the most common nonmotor symptoms of Parkinson's disease, occurring in approximately 35% of patients.

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used medications to treat depression in Parkinson's disease in clinical practice. However, several studies suggested that all SSRIs may not be more effective than placebo in this situation. Positive results in randomized clinical trials have been demonstrated for nortriptyline, desipramine, venlafaxine, citalopram and paroxetine.

There is a suggestion that noradrenergic or dual action (noradrenergic / serotoninergic) antidepressants may be more effective for treating depression in Parkinson's disease than SSRIs.

Antiparkinsonian medications can also exert an antidepressant effect e.g. Pramipexole & selegiline.

Preliminary studies suggest that repetitive transcranial magnetic stimulation (rTMS) may be effective for depression in Parkinson disease. Electroconvulsive therapy (ECT) can be considered for refractory moderate to severe depression.

Psychotic symptoms (hallucinations or delusions)

Antiparkinsonian drugs can trigger psychosis in patients with Parkinson's disease. In Parkinson's

disease patients with psychosis, antiparkinsonian medications other than levodopa should be withdrawn in an effort to resolve psychosis while maintaining motor control with levodopa. In individuals with only mild hallucinations that are well tolerated, active antipsychotic treatment may not be necessary.

Pimavanserin was approved in April 2016 for treatment of hallucinations and delusions associated with Parkinson's disease psychosis. It is the first drug to be approved for this condition. It is a selective serotonin inverse agonists (SSIA). It not only preferentially targets 5-HT2A receptors, but also avoids activity at dopamine and other receptors commonly targeted by antipsychotics.

Use of some other typical antipsychotics can exacerbate motor symptoms of Parkinson's disease and should be avoided.

Quetiapine is the atypical neuroleptic agent most commonly used by movement-disorder experts, because it rarely exacerbates motor symptoms and blood monitoring is not required. Quetiapine is used in Parkinson's disease at doses much lower than those used in schizophrenia.

Clozapine can also be used, but blood monitoring is required due to its potential for agranulocytosis and other severe side effects. For this reason, clozapine is usually reserved for patients who are not adequately controlled with quetiapine.

Anxiety

The 2010 American Academy of Neurology (AAN) practice parameter on the treatment of nonmotor symptoms in Parkinson's disease found insufficient evidence to support or refute the treatment of anxiety in Parkinson's disease with levodopa. However, SSRIs and venlafaxine may be beneficial. Buspirone is well tolerated but has not been studied in this population. Benzodiazepines can be considered, but adverse effects such as cognitive impairment, somnolence and balance problems may be concerning. Behavior modification techniques can play an important role in the treatment of anxiety.

Impulse behaviors

Cognitive-behavioral therapy (CBT) can help control impulse behaviors in PD. In a study of 45 patients with idiopathic PD and associated impulse control behaviors that had not responded to standard treatment, CBT significantly improved symptom severity, neuropsychiatric disturbances and depression and anxiety levels.

In a placebo-controlled pilot study of 50 patients with idiopathic PD who developed impulse control disorder (ICD) symptoms while receiving dopamine agonist treatment, researchers found that the opioid antagonist naltrexone improved ICD symptoms, as measured on a PD-specific rating scale.

Sleep disturbances

Benzodiazepines can be helpful in the treatment of rapid eye movement (REM) sleep behavior disorder (RBD) and obstructive sleep apnea (OSA) can be treated with positive airway pressure with either continuous pressure or bilevel pressure. Sleep hygiene techniques include avoiding stimulants/fluids near bedtime, avoiding heavy late-night meals and following a regular sleep schedule. It is advised that patients with Parkinson's disease and sudden-onset sleep avoid driving and take precautions against potential occupational hazards.

The 2010 AAN practice parameter found insufficient evidence to support or refute beneficial effects from the treatment of RBD in Parkinson's disease. Other sleep disorders may benefit from treatment. Levodopa/carbidopa should be considered to treat periodic limb movements of sleep. Modafinil may improve patients' subjective perceptions of excessive daytime somnolence (EDS) and methylphenidate may be considered in patients with fatigue.

Exercise and Physical Therapy

Exercise therapy in patients with Parkinson's disease using a variety of physiotherapy interventions may play a role in improving gait, balance and flexibility, aerobic capacity, initiation of movement and functional independence. There has been a resurgence of interest in the potential benefit of exercise in Parkinson's disease, including a possible neuroprotective effect. Vigorous exercise in mid-life is associated with a reduced risk of subsequent Parkinson's disease.

In animal models, vigorous exercise provides a protective effect against a variety of toxins that cause parkinsonism. In addition, in healthy people, serum

brain-derived neurotrophic factor (BDNF) increases after exercise, in proportion to the intensity of the activity.

In Parkinson's disease, BDNF levels in the substantia nigra are reduced and in animal models of Parkinson's disease, BDNF provides a neuroprotective effect. This is an area of active research.

Speech Therapy

During the course of the disease, 45-89% of patients report speech problems and more than 30% find speech problems to be the most debilitating part of the disease. Medications and surgery cannot effectively treat the laryngeal manifestations of Parkinson's disease. For this reason, speech therapy plays a key role in the disease's vocal treatment regimen. Speech therapy is effective in treating the laryngeal manifestations of Parkinson's disease, but despite the significant number of patients with vocal symptoms, only an estimated 3-4% of patients with Parkinson's disease undergo speech therapy.

The Lee Silverman Voice Treatment (LSVT) is a program designed to increase vocal intensity in patients which is so far the most promising therapy for Parkinson's disease laryngeal symptoms.

Dietary Considerations

Proper nutritional support is essential, including adequate dietary fiber to prevent the common problem of constipation.

Patients recently diagnosed with Parkinson's disease are often confused regarding dietary protein, because they receive conflicting information.

Levodopa is absorbed via a large neutral amino acid active carrier system and therefore competes with dietary proteins for absorption; this effect is generally relatively small and is not clinically important for most patients, especially those with early or moderate disease.

However, as the disease progresses and patients become more and more sensitive to maintaining relatively narrow therapeutic serum concentrations of levodopa, this effect can become clinically relevant. These patients may benefit from a low protein or a protein redistributed diet. In a low-protein diet, the total daily protein intake is spread more or less equally over the day. In a protein-redistributed diet, individuals only consume food very low in protein during the day and then eat a high-protein meal in the evening.

In patients with early disease, the primary concern regarding levodopa is typically nausea, which is less likely to occur if they take their levodopa dose at the completion of meals. Therefore, in early Parkinson's disease, it is common to instruct patients to take their levodopa after meals to reduce the likelihood of nausea as the dose is titrated to clinical effect.

Vitamin E and coenzyme Q10 have not been shown to have a neuroprotective effect in Parkinson's disease and they are not currently recommended as dietary supplements for this condition.

Consultations

Generally, patients with Parkinson's disease are best treated and monitored by a neurologist or movement disorder specialist. Depending on the patient, consultations may include the following:

- ❏ Neurosurgeon
- ❏ Psychiatrist
- ❏ Urologist
- ❏ Physiatrist
- ❏ Nutritionist
- ❏ Otolaryngologist
- ❏ Gastroenterologist
- ❏ Speech therapist

Long-Term Monitoring

Patients with Parkinson's disease must have regular follow-up care to ensure adequate treatment of motor and behavioral abnormalities. Once patients are stable on a medication regimen, provide follow-up care at least every 3-6 months and periodically adjust medication dosages as necessary.

Patients also need to be monitored for adverse events, including somnolence, sudden-onset sleep, impulse control disorders and psychosis. In addition, patients should be evaluated and treated for emergence of clinically relevant nonmotor symptoms, including dementia, psychosis, sleep disorders and mood disorders.

Medication Summary

Dopamine agonists

Dopamine agonists are effective as monotherapy in early PD and as adjuncts to levodopa/PDI (peripheral decarboxylase inhibitor) in moderate to advanced disease. Dopamine agonists directly stimulate postsynaptic dopamine receptors to provide antiparkinsonian benefit. All available dopamine agonists stimulate D2 receptors an action that is thought to be clinically beneficial.

The role of other dopamine receptors is currently unclear.

Dopamine agonists are effective to treat motor features of early PD and they cause less develop-ment of motor fluctuations and dyskinesia than levodopa. For patients with motor fluctuations on levodopa/PDI, the addition of a dopamine agonist reduces off time, improves motor function and allows lower levodopa doses. Examples are: Carbidopa/levodopa, Apomorphine, Pramipexole, Ropinirole, Amantadine and Rotigotine.

Anticholinergic

Anticholinergics are commonly used as symptomatic treatment of PD, both as monotherapy and as part of combination therapy. Anticholinergic agents provide benefit for tremor in approximately 50% of patients but do not substantially improve bradykinesia or rigidity. If one anticholinergic does not work, another shoulb be tried. Examples are: Trihexyphenidyl and Benztropine mesylate.

MAO-B inhibitors

MAO-B inhibitors inhibit the activity of MAO-B oxidases that are responsible for inactivating dopamine. Examples are: Selegiline and Rasagiline.

Acetylcholinesterase inhibitors, Central

Pathologic changes in dementia associated with PD involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways may be involved in memory, attention, learning and other cognitive processes. Acetylcholinesterase inhibitors may exert their therapeutic effect by enhancing cholinergic function through inhibition of acetylcholinesterase. Examples are: Donepezil, Rivastigmine and Galantamine.

NMDA antagonists

Persistent activation of CNS N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of dementia. Agents such as memantine, which is an NMDA receptor antagonist, can prevent activation of the NMDA receptors. Examples is: Memantine

COMT inhibitors

Catechol-O - methyl transferase (COMT) inhibitors inhibit the peripheral metabolism of levodopa, making more levodopa available for transport across the blood-brain barrier over a longer time. For patients with motor fluctuations on levodopa/carbidopa, the addition of a COMT inhibitor decreases off time, improves motor function and allows lower levodopa doses. Examples are:

Tolcapone, Entacapone and combination of Carbidopa+levodopa+entacapone.

Selective Serotonin Inverse Agonists (SSIA)

SSIAs preferentially target 5-HT2A receptors, but does not affect activity of dopamine and other receptors commonly targeted by antipsychotics. Example is: Pimavanserin.

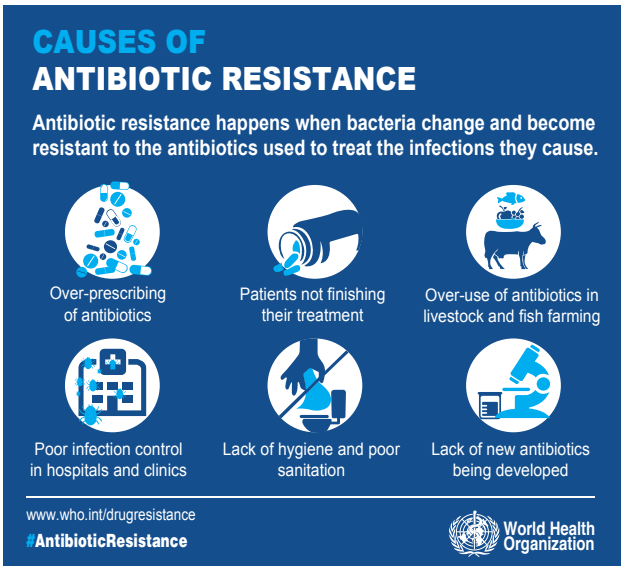
References:

❏ emedicine.medscape.com

❏ neuroendoimmune.wordpress.com

Superbug infections are resistant to most anitbiotics and are therefore difficult to treat. Each year, superbugs infect more than 2 million people and kill at least 23,000 people nationwide in USA. With such a large number of people being affected by superbug infections each year, it is vital to take precautions to prevent them from spreading.

Patients are often admitted to the hospital with compromised microbiomes and weakened immune systems. The addition of more antibiotics allows these lurking, resistant superbugs to take control of the patient. As increasing use of antibiotics depletes the good microbes in the individual's gut, superbugs are able to destroy the balance and take over the patient's immune system. When there are not enough protective microbes in the gut, the superbug can take command and an infection manifests. The real threat of super bugs is their ability to manifest when a patient is given antibiotics.



Plasmids are swapped in the gut of humans, as bacteria interact. If the individual obtains a bacterium with a plasmid that carries resistance to colistin, the bacteria may lurk in the gut and be held in check; however, the bacterium becomes infectious when antibiotics are administered. The antibiotics kill everything except for the resistant bacteria. This failure of modern medicine allows the newly-equipped super bug to fill the void and manifest infection in the body. With no microbial competition to hold the infectious bacterium accountable, the super bug takes control.

Scientists warn that a single bacterium might collect multiple plasmids with multiple genes for resistance to multiple antibiotics. These infections can occur for multiple types of bacteria; tests have shown that *E. coli* has developed resistance through this same mcr-1 gene. One of the most recent super bugs to manifest came from the overuse of an antibiotic class called carbapenems. In 2009, scientists quickly found that the super bug had developed resistance through the gene, NDM-1, which allowed the bacteria to survive against the antibiotics that were once so heavily relied upon to treat it.

The real threat here is not the spread of a super bug from one person to the next. The real problem is the weakening of microbiomes via antibiotics which allows isolated cases of super bug infection to manifest, time and time again, in new places. Even if a hospital can control a super bug in the moment through isolation and sterilization, the real threat could manifest again and again, somewhere else.

Clostridium difficile

Prolonged use of antibiotics can allow this common intestinal inhabitant to explode into a lethal infection as the drugs kill off its beneficial rivals in the human gut. Spread via hospital surfaces and human contact, *C. difficile* most often affects the elderly. It causes severe diarrhea and can damage the colon and it has become very difficult to treat.

- ❏ CDC threat category: Urgent
- ❏ CDC death estimate: 15,000
- ❏ Statistical uncertainty of CDC estimate: 7,600 to 20,000
- ❏ Gram positive

Carbapenem-resistant *Enterobacteriaceae* (CRE)

Drug-resistant members of this family of Gram-negative bacteria are spread largely in healthcare settings. Strains of some species in the group, including *Escherichia coli, Enterobacter aerogenes, Enterobacter cloacae* and *Klebsiella pneumoniae,* are resistant to antibiotics called carbapenems, considered one of the last lines of defense against such infections. When carbapenems fail, doctors are often forced to turn to colistin, a decades-old drug that can have toxic side effects - and some CRE strains are already showing resistance to that drug, too.

- CDC threat category: Urgent
- CDC death estimate: 610
- Statistical uncertainty of CDC estimate: 180 to 1,200
- Gram negative

Drug-resistant *Neisseria gonorrhoeae*

Some strains of this sexually transmitted infection, which can cause painful urination and inflammation in the pelvis, have developed resistance to the drugs commonly used to treat it.

- CDC threat category: Urgent
- CDC death estimate: Fewer than 5
- Statistical uncertainty of CDC estimate: Not calculated
- Gram negative

Multidrug-resistant *Acinetobacter*

Acinetobacter baumannii and other members of this genus are typically found in soil and water, and can survive on human skin and on medical equipment. They can cause pneumonia, urinary tract infections and serious blood or wound infections.

- CDC threat category: Serious
- CDC death estimate: 500
- Statistical uncertainty of CDC estimate: 140 to 920
- Gram negative

Drug-resistant *Campylobacter*

This bug infects humans through contaminated milk, water or food - especially poultry - causing diarrhea, cramps and fever.

- CDC threat category: Serious
- CDC death estimate: 28
- Statistical uncertainty of CDC estimate: 0 to 120
- Gram negative

Fluconazole-resistant *Candida*

Candida is a fungus, not a bacterium. The CDC included it on its list because strains of the fungus are increasingly showing resistance to the drugs commonly used to treat it. *Candida* is present in many people without doing harm, but it can because serious infections in patients with weakened immune systems or if introduced into the bloodstream.

- CDC threat category: Serious
- CDC death estimate: 220
- Statistical uncertainty of CDC estimate: 65 to 430

Extended spectrum β-lactamase producing *Enterobacteriaceae* (ESBLs)

These bacteria, including strains of *Escherichia coli* and *Klebsiella pneumoniae,* produce an enzyme that destroys many antibiotics. They most often manifest as urinary tract infections, but can also cause serious bloodstream and lung infections. They are spread through improperly washed hands, surfaces and medical equipment. Some of the ESBL *E. coli* strains are also foodborne.

- CDC threat category: Serious
- CDC death estimate: 1,700
- Statistical uncertainty of CDC estimate: 500 to 3,300
- Gram negative

Vancomycin-resistant *Enterococcus* (VRE)

Enterococci normally live in human intestines and the female genital tract without issue, but they can lead to serious infection when they spread through urinary or intravenous catheters or enter the bloodstream. Some strains have developed resistance to vancomycin, one of the most powerful antibiotics available.

- CDC threat category: Serious
- CDC death estimate: 1,300
- Statistical uncertainty of CDC estimate: 390 to 2,600
- Gram positive

Multidrug-resistant *Pseudomonas aeruginosa*

This pathogen thrives in moist environments and mostly affects hospital patients, especially those using mechanical ventilation or catheters or with surgical or burn wounds. The Gram-negative bacteria are exceptionally difficult to treat as they have developed resistance to multiple classes of drugs in addition to their broad natural resistance.

- CDC threat category: Serious
- CDC death estimate: 440
- Statistical uncertainty of CDC estimate: 130 to 850
- Gram negative

Drug-resistant non-typhoidal *Salmonella*

Non-typhoidal *Salmonella* is a common foodborne pathogen that causes more dangerous infection when it is resistant to common antibiotics. It causes severe, sometimes bloody diarrhea, cramps and fever.

- CDC threat category: Serious
- CDC death estimate: 40
- Statistical uncertainty of CDC estimate: 0 to 120
- Gram negative

Drug-resistant *Salmonella typhi*

A member of the Enterobacteriaceae family, these bacteria spread through contaminated food or water or through person-to-person contact. Typhoid fever, rare in developed countries, can lead to serious health complications and death if untreated.

- CDC threat category: Serious
- CDC death estimate: Fewer than 5
- Statistical uncertainty of CDC estimate: Not calculated
- Gram negative

Drug-resistant *Shigella*

Shigella mostly affects young children and is spread through hand contact, food or water. In the U.S., a drug-resistant strain of the infection, which causes painful diarrhea, has been spread largely by travelers and spreads especially quickly in childcare settings and among homeless people and gay and bisexual men.

- CDC threat category: Serious
- CDC death estimate: Fewer than 5
- Statistical uncertainty of CDC estimate: Not calculated
- Gram negative

Methicillin-resistant *Staphylococcus aureus* (MRSA)

S. aureus is a once-routine infection that has become resistant to several powerful antibiotics. It most often occurs as a localized skin infection, but can become deadly if it enters the lungs or bloodstream, often through surgery or medical equipment. It is widely present in both healthcare settings and among the general population.

- CDC threat category: Serious
- CDC death estimate: 11,000
- Statistical uncertainty of CDC estimate: 8,000 to 17,000
- Gram positive

Drug-resistant *Streptococcus pneumoniae*

S. pneumoniae can cause pneumonia; ear, sinus and bloodstream infections; and meningitis. Some strains are resistant to multiple drugs, which can be especially dangerous to young children, the elderly and HIV patients. It is spread person-to-person, often in childcare and healthcare facilities.

- CDC threat category: Serious
- CDC death estimate: 7,000
- Statistical uncertainty of CDC estimate: Not calculated
- Gram positive

Drug-resistant *Tuberculosis*

Mycobacterium tuberculosis is spread through the air and usually infects the lungs, but can also infect organs such as the brain or kidneys. If caught early, the infection is largely treatable, but drug-resistant strains have emerged over the years. Some do not respond to many types of antibiotics and can be deadly in immunocompromised patients, such as those with HIV.

Vancomycin-resistant *Staphylococcus aureus* (VRSA)

These *S. aureus* infections are resistant to vancomycin, one of the most powerful antibiotics available. They most often occur as skin infections. They can become deadly if they manifest as bloodstream or lung infections, especially in people with pneumonia or on ventilators.

- CDC threat category: Concerning
- CDC death estimate: Fewer than 5
- Statistical uncertainty of CDC estimate: Not calculated
- Gram positive

Erythromycin-resistant Group A *Streptococcus*

Group A *Streptococcus* is the most common cause of strep throat in children and adults, and erythromycin is one of the most commonly used antibiotics to treat it. The infection is usually mild, but can sometimes be life-threatening. It is spread through contact with infected mucus or through skin wounds or sores.

- CDC threat category: Concerning
- CDC death estimate: 160

- Statistical uncertainty of CDC estimate: Not calculated
- Gram positive

Clindamycin-resistant Group B *Streptococcus*

In newborns, Group B *Streptococcus* is a common cause of sepsis, a potentially fatal blood infection. Adults are susceptible, too. The widespread use of antibiotics to prevent the infection in newborns has caused some strains of bacteria to develop resistance to the drug clindamycin.

- CDC threat category: Concerning
- CDC death estimate: 440
- Statistical uncertainty of CDC estimate: Not calculated
- Gram positive

Recommendation from Mission Critical: Preventing Antibiotic Resistance (CDC)

Recommendation for healthcare providers:

- **Antibiotic prescription:** Doctors should choose proper antibiotics based on clinical features and patients' blood culture report. They should reassess the prescription within 48 hours based on tests and patient exam.
- **Dosing schedule:** Healthcare providers should document the dose, duration and indication for every antibiotic prescription.
- **Awareness:** Physicians should stay aware of antibiotic resistance patterns in health facility.
- **Preventive measures:** All doctors should follow hand hygiene and other infection control measures with every patient.

Recommendation for Patients:

- **Health consciousness:** Patient should ask to physicians, whether appropriate tests will be done to make sure the right antibiotic is prescribed.
- **Duration of treatment:** Patient should take antibiotics exactly as the doctor prescribes. Skipped doses and incomplete prescribed course may lead to treatment failure and antibiotic resistance.
- **Treatment pattern:** They should not save antibiotics for the next illness and discard any left-over medication once the prescribed course of treatment is completed.
- **Self-medication:** Patient should not ask antibiotics when doctor thinks patient do not need them because antibiotics have side effects.
- **Preventive measures:** patients can easily prevent infections by practicing good hand hygiene and by getting recommended vaccines.

Recommendation for healthcare facility administrators and payers can:

Adopt an antibiotic stewardship program that includes, at a minimum this checklist:

- **Leadership commitment:** Dedicate necessary human, financial, and IT resources.
- **Accountability:** Appoint a single leader responsible for program outcomes. Physicians have proven successful in this role.
- **Drug expertise:** Appoint a single pharmacist leader to support improved prescribing.
- **Action:** Take at least one prescribing improvement action, such as requiring reassessment within 48 hours to check drug choice, dose, and duration.
- **Tracking:** Monitor prescribing and antibiotic resistance patterns.
- **Reporting:** Regularly report to staff prescribing and resistance patterns and steps to improve.
- **Education:** Offer education about antibiotic resistance and improving prescribing practices.

References:

- https://www.cdc.gov
- http://www.who.int/mediacentre/commentaries/stop-antibiotic-resistance/en/

Postmenopausal osteoporosis is a common disease with a spectrum ranging from asymptomatic bone loss to disabling hip fracture. Osteoporosis is defined as a disease of increased skeletal fragility accompanied by low bone mineral density (a T score for bone mineral density below -2.5) and microarchitectural deterioration. In the United States, there are 1.5 million osteoporotic fractures per year, with an annual direct cost of nearly $18 billion. It is predicted that the prevalence of fracture will increase by the year 2025, yet less than a quarter of all women who sustain an osteoporotic fracture currently receive appropriate treatment for osteoporosis.

Fractures occur because of qualitative and quantitative deterioration in the trabecular and cortical skeleton. Bone quality cannot be measured clinically, but bone mineral density can be measured painlessly, quickly, safely, accurately, precisely and relatively inexpensively; several methods are available, of which dual-energy x-ray absorptiometry is currently the most validated. Low bone mass at any skeletal site is associated with a substantially increased risk of fracture. Other risk factors include advancing age, low body weight, maternal history of osteoporosis, the direction of a fall (a fall backward and to one side is most likely to result in a fracture), and most important, the presence of a previous fracture.

Pathophysiology

Once an adult reaches maturity, skeletal growth ceases. Yet there is continuous replacement of old bone with new throughout life. The underlying mechanism of bone loss is a disturbance of this bone remodelling process. There is increased cellular removal of bone and relatively decreased replacement of bone and consequent reduction in the biomechanical competence of the skeleton. The remodelling process occurs at discrete areas of activity along the bone surface.

There are 5 phases to bone remodelling:

1. Activation: An unknown signal attracts precursor cells (preosteoclasts) to a potential remodelling site. Preosteoclasts fuse to form osteoclasts, the multinucleated giant cells responsible for bone removal or resorption.
2. Resorption: Osteoclasts erode bone, forming a cavity on the bone surface in cancellous bone and a tunnel in cortical bone. Osteoclasts then disappear. Their fate is unknown.
3. Reversal: Mononuclear cells of unknown lineage appear to prepare the surface for bone formation.
4. Formation: Osteoblasts, derived from mesenchymal cells are recruited to the surface of the cavity to replace as exactly as possible the recently removed bone. The newly synthetised matrix (osteoid) is mineralised by formation of calcium hydroxyapatite crystals between the collagen fibrils.
5. Quiescence: Bone tissue remains dormant, lined by resting osteoblasts until the next cycle of bone remodelling begins. The entire remodelling process occurs over approximately 4-8 months with a range of 3 months to 2 years.

Osteoporosis results from a basic abnormality in this bone remodelling:

1. At menopause, there is an increased activation of remodelling sites due to the reduction of the hormone oestrogen resulting in decrease of both trabecular and cortical bone. The greatest proportion of bone loss occurs in cancellous bone which is found in the vertebral bodies and metaphyses of long bones, thus accounting for the high incidence of fractures at these sites. So as ovarian function gradually declines, there is an equally gradual increase in the rate of bone loss.
2. Bone resorption is increased, resulting in deeper resorption cavities which may perforate trabecular plates.
3. With increasing age, formation of new bone tissue declines causing a permanent bone deficit at each remodelling cycle.

The exact mechanism by which oestrogen influences bone remodelling is not clear. A study suggested that absence of oestrogen rendered the skeleton more sensitive to the bone resorbing effects of parathyroid hormone. Specific receptors for oestrogens have also been identified in cells of the osteoblast lineage and the reduction in ovarian oestrogen will affect bone mass. Oestrogens may also control the synthesis and secretion of a variety of growth factors within bone, especially transforming.growth factor beta (TGF-b) and the insulin-like growth factors.

Women at Risk

Factors that predispose towards postmenopausal osteoporosis are those that induce (1) a low peak bone mass and (2) excessive postmenopausal and age-related bone loss.

These factors include genetic, endocrine and lifestyle components:

1. Caucasian and Asian women who are thin or petite with a previous family history of the disease
2. Women who experience an early menopause
3. Women with low premenopausal oestrogen levels
4. Insufficient calcium intake in the diet
5 Cigarette smoking may interfere with oestrogen metabolism premenopausally and render postmenopausal HRT less effective
6. Alcohol abuse
7. Sedentary lifestyle

Diagnosis

1. X-rays can detect osteoporosis when about 30% bone loss has occurred causing fractures and decreased radiodensity, accentuation of primary and loss of secondary trabeculae in vertebral bodies and thining and accentuation of the cortices.
2. Radiogrammetry in which the thickness of the cortex of metacarpal or phalangeal bones is measured on standard radiographs of the hand. This is useful in large study populations to predict fractures.
3. Radiographic absorbtiometry measures the density of phalanges or metacarpals and compared with the density of an aluminium reference wedge using either an optical densitometer or videodensitometer.
4. Single photon absorbtipmetry (SPA) measures the photon attenuation of the measured site (radius) and converted to bone mineral content BMC in grams. SPA is confined to appendicular skeleton.
5. Dual photon absorbtiometry (DPA) is used for bone mass measurements in the central skeleton or total body bone mineral content and fat content assessment. Bone mass estimates are given as BMC in grams or as BMD in grarns/sq cm.
6. Dual x-ray absorbtiometry (DXA) is the modem upgraded version of DPA where the radioisotope source is replaced by an X-ray source. This enables bone density to be measured at the hip or spine with greater precision. DXA technology has gained widespread acceptance and distribution.
7. Quantitative computed tomography (QCT) is the only method that can estimate bone density separately in the trabecular and cortical bone compartments and the only method giving a true density (in mg/sq cm) estimate. Usually the vertebral body is the site of measurement.
8. Ultrasound measurement of bone density is confined to the appendicular skeleton and made at the OS calcis and the patella. The advantage of ultrasound is its absence of radiation.
9. Neutron activation analysis is a method of measuring total body calcium by irradiating the body with thermal neutrons and examining the spectrum of g-rays that results. The availability of this method is limited.
10. Urinary hydroxyproline is a product of collagen breakdown and approximately 10% of the total production is excreted in the urine as the peptide-bound form. Pyrilinks- D is a highly sensitive urine test that measures deoxypyridinoline (Dpd) a cross link of type I collagen present in bone. It is excreted unmetabolised in urine and is highly sensitive specific marker of bone resorption. It can help to identify bone loss early in menopause.

Risk Assessment & Management

A comprehensive management plan for osteoporosis includes evaluation of those at highest risk, exclusion of secondary causes of low bone mineral density, and selection of the appropriate treatment. A history of fragility fractures (unrelated to substantial trauma) in a postmenopausal woman strongly supports a diagnosis of osteoporosis, regardless of bone mineral density. Secondary causes such as primary hyperparathyroidism, vitamin D deficiency due to low intake, lack of exposure to sunlight or malabsorption, and multiple myeloma should be excluded. Biochemical markers of bone turnover such as N-telopeptide or osteocalcin rarely help in establishing a diagnosis or selecting treatment, although they

may be useful in determining whether there is accelerated bone loss, particularly during the first few years of menopause. Decision making should also take into account several caveats. Osteoporosis therapy can reduce the risk of fracture by as much as 50 percent, but some women have fractures despite treatment. Also, changes in lifestyle and the use of pharmacologic interventions are lifetime commitments, and therefore cost, compliance with a medication regimen, and safety must be considered in decisions on therapy. Moreover, a substantial percentage of osteoporotic fractures occur in women who have T scores above -2.5. (A T score is the number of standard deviations the bone-mineral-density measurement is above or below the young-normal mean bone density.) In some cases, there is a substantial discrepancy between the spine and hip T scores. Thus, decisions with regard to treatment should not be based solely on bone mineral density.

Nonpharmacologic Options:

Calcium supplementation should be adjunctive treatment for all women with established osteoporosis and must be part of any preventive strategy to ameliorate bone loss. Increased calcium intake reduces the hyperparathyroidism associated with advancing age and can enhance mineralization of newly formed bone. A total calcium intake of 1200 to 1500 mg per day (through diet, supplements, or both) is recommended for all postmenopausal women.

Vitamin D is essential for skeletal maintenance and enhancement of calcium absorption. Dietary insufficiency of this vitamin is a growing problem with as many as two thirds of patients with hip fracture classified as having a deficiency of vitamin D level below 15 ng per milliliter. Elderly persons with chronic conditions that require assisted-living situations are particularly vulnerable to vitamin D deficiency because of lack of adequate exposure to sunlight. One large trial showed a reduction of 33 percent in hip fracture among nursing home residents who were randomly assigned to receive calcium supplements and vitamin D, as compared with those given placebo. There is strong evidence that vitamin D supplementation enhances muscle strength and reduces the risk of falling.

Counseling with regard to avoidance of smoking and excessive alcohol intake is routinely warranted, particularly since smoking and alcohol intake have been linked in some studies to greater fracture risk.

Bed rest or immobility due to other causes can result in rapid bone loss. Moreover, the number of falls and the percentage of falls that result in fracture increase with age. Regular physical activity, including aerobic, weight-bearing, and resistance exercise, is effective in increasing bone mineral density of the spine and strengthening muscle mass in postmenopausal women, but there are no large trials establishing whether these interventions reduce the fracture risk.

Pharmacologic Therapies:

Pharmacologic agents for the treatment of osteoporosis can be classified as either antiresorptive (i.e., targeting osteoclast-mediated bone resorption) or anabolic (i.e., stimulating osteoblasts to form new bone). Drugs of each type have been shown to improve BMD and reduce the risk of fractures.

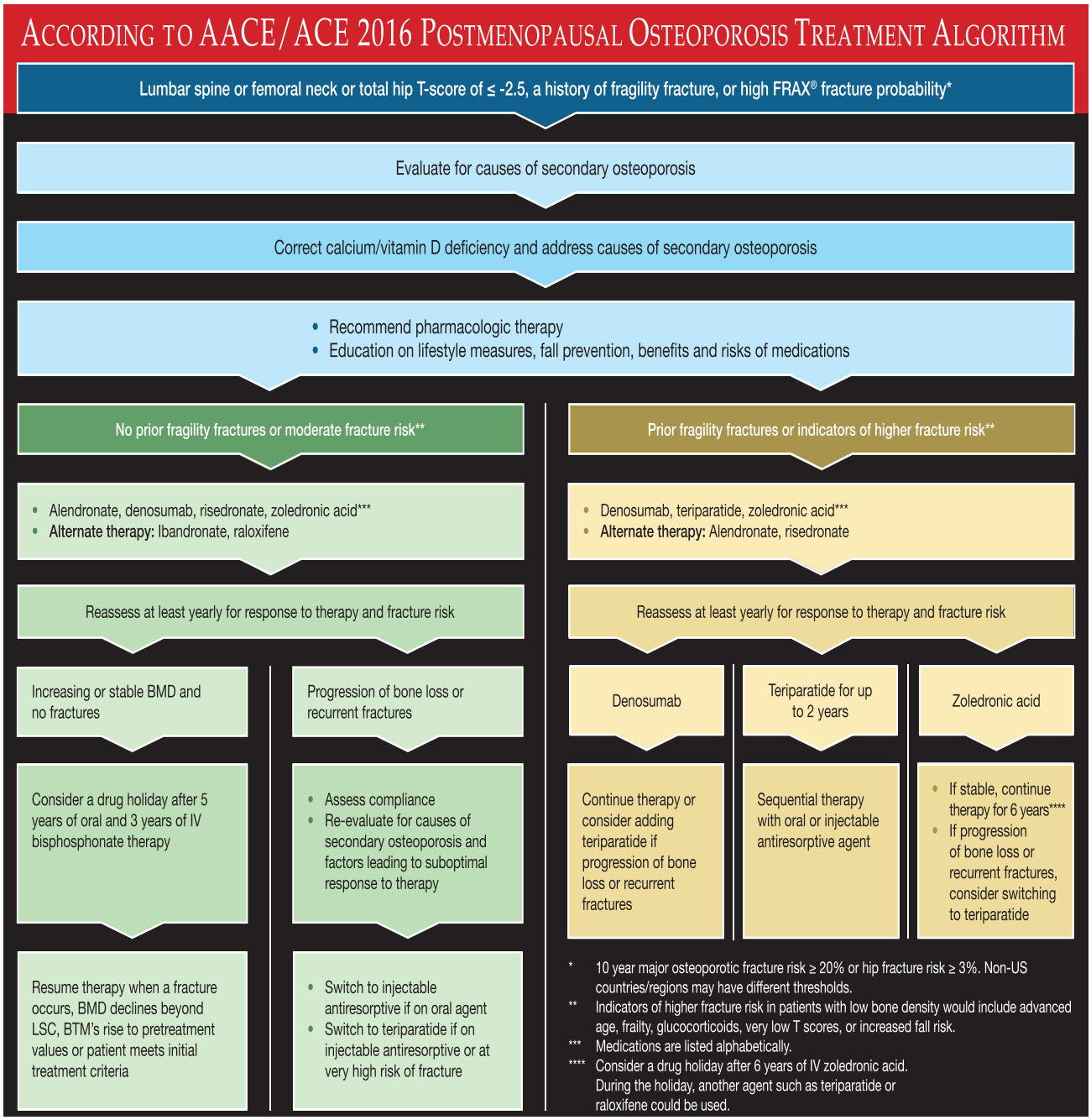
Estrogen and Selective Estrogen-Receptor Modulators:

Estrogen treatment, with or without progesterone, has direct effects on osteocytes, osteoclasts, and osteoblasts, leading to inhibition of bone resorption and maintenance of bone formation. Both low-dose conjugated estrogens and ultra-low-dose estradiol, which are often used in the short term for postmenopausal symptoms, increase BMD, but their antifracture efficacy has not been established. Concerns about nonskeletal risks associated with estrogen use (e.g., breast cancer and coronary, cerebrovascular and thrombotic events) have led to recommendations against using estrogen as a first-line therapy for osteoporosis.

Selective estrogen-receptor modulators (SERMs) activate distinct tissue receptors for estrogen. Raloxifene is a SERM that has been approved by the FDA to treat osteoporosis; it inhibits bone resorption, increases spine BMD slightly and decreases the risk of vertebral fractures by 30% but has no effect on nonvertebral or hip fractures. Long-term use of raloxifene decreases breast-cancer risk among high-risk women but increases the risk of thromboembolic events.

Recently, the combination of another SERM, bazedoxifene, with estrogen was approved by the FDA for the treatment of menopausal symptoms and the prevention of osteoporosis but not for the treatment of osteoporosis.

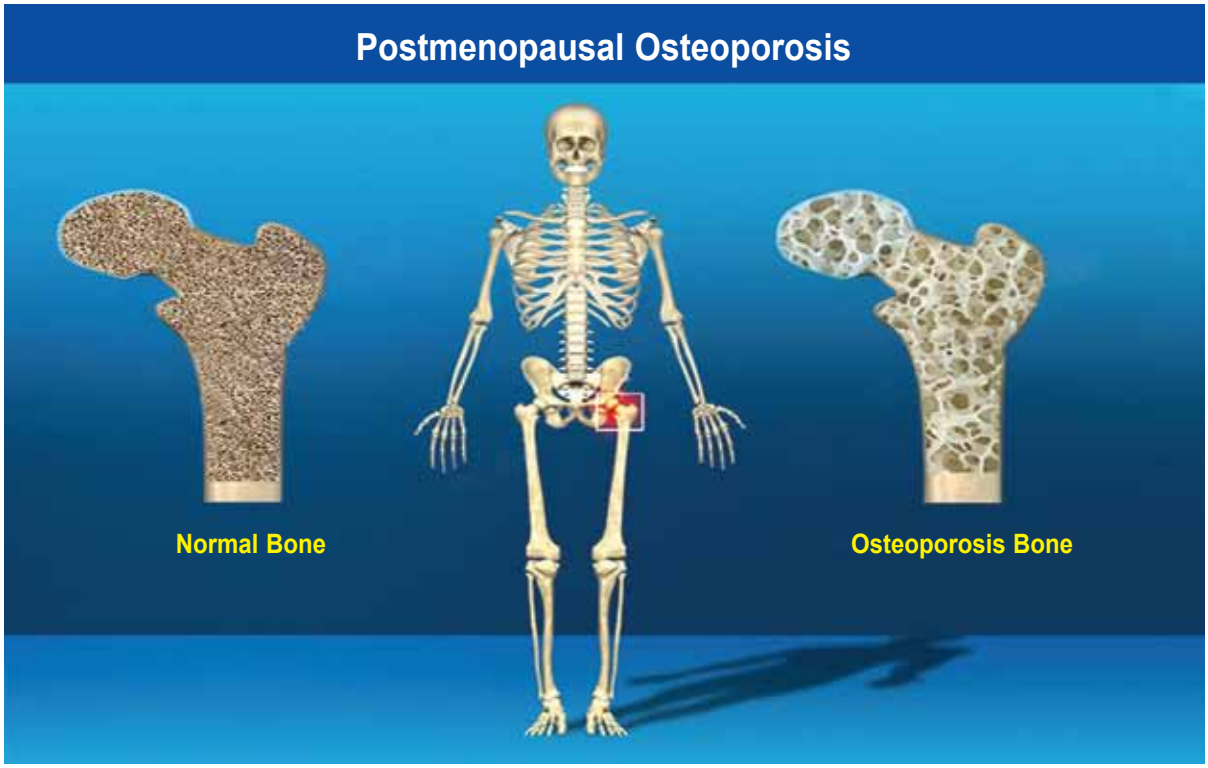
AACE/ACE Treatment Algorithm:



Bisphosphonates:

Nitrogen-containing bisphosphonates (alendronate, risedronate and zoledronic acid) provide antiresorptive effects by binding to the calcium hydroxyapatite crystal at sites of bone resorption, where the bone matrix is exposed. The bisphosphonate is buried under the newly formed bone, where it lies inert and has no skeletal effects. During bone resorption the drug is released from the bone matrix and ingested by osteoclasts. It inhibits farnesyl diphosphate synthase (FDPS), a key enzyme in the cholesterol synthesis pathway involved in post-translational modification of important signalling molecules. This inhibition disrupts several pathways involved in cytoskeletal organization, cell survival and cell proliferation,

leading to osteoclast deactivation and apoptosis. The result is reduced bone turnover and enhanced bone mineralization because of the extended time available for mineral accumulation.



Denosumab:

Denosumab was the first biologic therapy approved to treat osteoporosis. Its action is distinct from that of bisphosphonates: it inhibits bone resorption by binding to the receptor activator of nuclear factor- kβ ligand (RANKL), thereby decreasing the differentiation of osteoclasts. Unlike bisphosphonates, it can be used in women with compromised renal function. A large trial involving women with a BMD T score of less than -2.5 but not less than -4.0 at the lumbar spine or total hip showed that treatment with denosumab (60 mg administered twice yearly by subcutaneous injection) resulted in a significantly lower risk of vertebral fractures (by 68%), hip fractures (by 40%) and nonvertebral fractures (by 20%) than the risk with placebo. As with bisphos-phonates, rare cases of atypical femur fractures and osteonecrosis of the jaw have been observed with denosumab treatment.

Teriparatide

Teriparatide is an anabolic agent that works primarily by increasing bone formation rather than by decreasing resorption. In a 21-month trial involving women with low BMD and previous vertebral fractures, teriparatide (20 μg per day) was associated with a lower risk of vertebral fractures (by 65%) and nonvertebral fractures (by 35%) than the risk with placebo, but not with a lower risk of hip fractures. Teriparatide is administered by daily self-injection and is approved for up to 2 years of use. Studies of its use after bisphosphonate treatment have shown that it retains its anabolic properties, although its action is slightly blunted. After teriparatide is discontinued, its benefits are quickly lost, so it should be followed by an antiresorptive agent. There is a risk of osteosarcoma associated with teriparatide treatment, on the basis of studies of long-term, high dose teriparatide in rodents, but only one documented case has been reported in more than 1 million human users.

References :

- ❏ AACE/ACE 2016
- ❏ www.nejm.org
- ❏ J Obstet Gynaecol Can 2014
- ❏ Malaysian J Pathol

Type 1 Diabetes in Children

Type 1 diabetes in children, previously called juvenile diabetes, occurs when the pancreas is unable to produce insulin. Since insulin is not present, sugar cannot travel from the blood into the cells and high blood sugar levels can result unless they are treated.

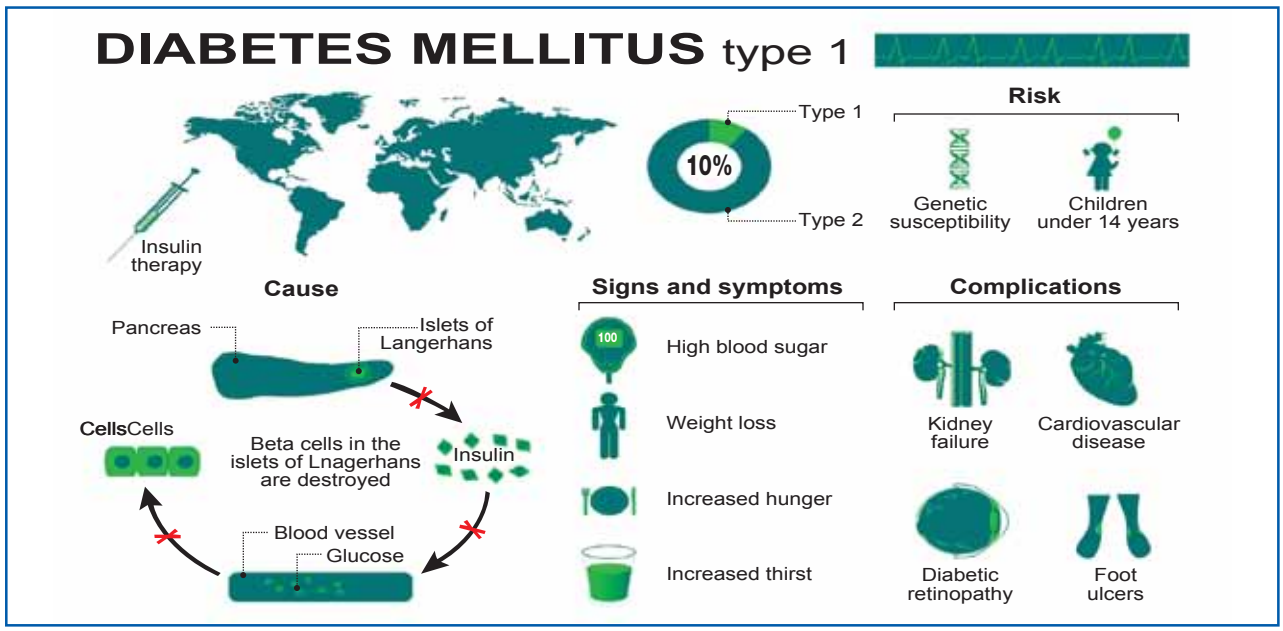
Children with the condition require lifelong insulin injections and blood sugar monitoring, with diet and exercise management to help keep blood sugar levels within their target range.

Symptoms

There are a number of early symptoms that suggest a child might have type 1 diabetes.

Early symptoms

- ❏ Frequent urination in large amounts (polyuria)
- ❏ Increase in thirst (polydipsia)
- ❏ Dry mouth or throat
- ❏ Weight loss
- ❏ Increase in appetite (polyphagia)



Epidemiology

Type 1 diabetes makes up an estimated 5-10% of all diabetes cases or 11-22 million worldwide. In 2006 it affected 440,000 children under 14 years of age and was the primary cause of diabetes in those less than 10 years of age. The incidence of type 1 diabetes has been increasing by about 3% per year.

Rates vary widely by country. In Finland, the incidence is a high of 57 per 100,000 per year, in Japan and China a low of 1 to 3 per 100,000 per year, and in Northern Europe and the U.S., an intermediate of 8 to 17 per 100,000 per year.

In the United States, type 1 diabetes affected about 208,000 youths under the age of 20 in 2015. Over 18,000 youths are diagnosed with Type 1 diabetes every year. Compared to non-Hispanic whites, Asian Americans, Hispanic Americans and Hispanic-Black Americans have greater odds of being diagnosed with diabetes.

- ❏ Feeling tired or weak

Other symptoms in toddlers or infants

- ❏ Diaper rash that doesn't improve with medicated cream

More serious symptoms

These symptoms appear if the diabetes is not treated or in some cases when it is undiagnosed.

- ❏ Weight loss
- ❏ Stomach aches
- ❏ Nausea and vomiting
- ❏ Heavy, rapid breathing (Kussmaul breathing)
- ❏ Drowsiness

Causes

The exact cause of type 1 diabetes is unknown. Scientists do know that in most people with type 1 diabetes the body's own immune system - which normally fights harmful bacteria and viruses - mistakenly destroys the insulin-producing (islet) cells in the pancreas.

Genetics may play a role in this process and exposure to certain viruses may trigger the disease.

There aren't many known risk factors for type 1 diabetes, though researchers continue to find new possibilities.

Known Risk Factors

- A family history: Anyone with a parent or siblings with type 1 diabetes has a slightly increased risk of developing the condition.
- Genetic susceptibility: The presence of certain genes indicates an increased risk of developing type 1 diabetes. In some cases - usually through a clinical trial - genetic testing can be done to determine if a child who has a family history of type 1 diabetes is at increased risk of developing the condition.

Possible Risk Factors

- Viral exposure: Exposure to Epstein-Barr virus, coxsackie virus, rubella or cytomegalovirus may trigger the autoimmune destruction of the islet cells or the virus may directly infect the islet cells.
- Low vitamin D levels: Research suggests that vitamin D may protect against type 1 diabetes. However, early intakes of cow's milk - a common source of vitamin D - have been linked to an increased risk of type 1 diabetes.
- Other dietary factors: Drinking water that contains nitrates may increase the risk of type 1 diabetes. The timing of the introduction of cereal into a baby's diet also may affect a child's risk of type 1 diabetes. One clinical trial found that between ages 4 and 7 months appears to be the optimal time for introducing cereal.

Complications

Type 1 diabetes can affect nearly every major organ in child's body, including the heart, blood vessels, nerves, eyes and kidneys. The good news is that keeping child's blood sugar level close to normal most of the time can dramatically reduce the risk of these complications.

Long-term complications of type 1 diabetes develop gradually. Eventually, if blood sugar levels aren't well-controlled, diabetes complications may be disabling or even life-threatening.

- **Heart and blood vessel disease:** Diabetes dramatically increases child's risk of various cardiovascular problems - including coronary artery disease with chest pain (angina), heart attack, stroke, narrowing of the arteries (atherosclerosis) and high blood pressure - later in life.
- **Nerve damage (neuropathy):** Excess sugar can injure the walls of the tiny blood vessels (capillaries) that nourish child's nerves, especially in the legs. This can cause tingling, numbness, burning or pain. Nerve damage usually happens gradually over a long period of time.
- **Kidney damage (nephropathy):** Diabetes can damage the numerous tiny blood vessel clusters that filter waste from blood. Severe damage can lead to kidney failure or irreversible end-stage kidney disease, requiring dialysis or a kidney transplant.
- **Eye damage:** Diabetes can damage the blood vessels of the retina (diabetic retinopathy). Diabetic retinopathy can cause blindness. Diabetes can also lead to cataracts and a greater risk of glaucoma.
- **Foot damage:** Nerve damage in the feet or poor blood flow to the feet increases the risk of various foot complications. Left untreated cuts and blisters can become serious infections.
- **Skin conditions:** Diabetes leave child more susceptible to skin problems, including bacterial infections, fungal infections and itching.
- **Osteoporosis:** Diabetes may lead to lower than normal bone mineral density, increasing child's risk of osteoporosis as an adult.

Diagnosis

To diagnose type 1 diabetes, below test are needed:

- **Glycated hemoglobin (A1C) test.** This blood test indicates average blood sugar level for the past two to three months. An A1C level of 6.5 percent or higher on two separate tests indicates diabetes.
- **Random blood sugar test.** A blood sample will be taken at a random time. Blood sugar values are expressed in milligrams per deciliter (mg/dL) or millimoles per liter (mmol/L). Regardless of when last ate, a random blood sugar level of 200 mg/dL (11.1 mmol/L) or higher suggests diabetes,

especially when coupled with any of the signs and symptoms of diabetes, such as frequent urination and extreme thirst.

- **Fasting blood sugar test.** A blood sample will be taken after an overnight fast. A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered pre-diabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests, indicates diabetes.

Blood tests to check for autoantibodies that are common in type 1 diabetes. These tests help to distinguish between type 1 and type 2 diabetes.

The presences of ketones - byproducts from the breakdown of fat - in urine also suggest type 1 diabetes, rather than type 2.

The Importance of Early Detection

Children with a delayed diagnosis of type I diabetes - can develop diabetic ketoacidosis (DKA). It is the leading cause of mortality in children with type 1 diabetes. If the body experiences a serious lack of insulin, it is unable to use glucose for energy. As a result, the body begins to break down fat for energy; this leads to the production of chemicals called ketones, which can be toxic at high levels. A build-up of these chemicals causes diabetic ketoacidosis (DKA), where the body becomes acidic. If diabetes is diagnosed early and managed effectively, diabetic ketoacidosis (DKA) is highly preventable.

Management of Type 1 Diabetes Mellitus

Management of type 1 diabetes is a lifelong commitment of blood sugar monitoring, insulin, healthy eating and regular exercise - even for kids. And as child grows and changes, so will his or her diabetes treatment plan. Over the years, child may need different doses or types of insulin, a new meal plan, or other treatment changes.

The American Diabetes Association recommends using patients age as are consideration in the establishment of glycerin goals with targets for preprandial, bedtime and hemoglobin A1C (HbA1C) levels.

Plasma blood glucose goal range (mg/dl)			
Values by age (years)	Before meals	Bedtime/overnight	A1C
Toddlers and preschoolers (0-6)	100-180	110-200	<8.5%
School age (6-12)	90-180	100-180	<8%
Addolescents and young adults (13-19)	90-130	90-150	<7.5%

Insulin therapy:

Patients with type 1 diabetes mellitus require lifelong insulin therapy most require 2 or more injections of insulin daily with doses adjusted on the basis of self monitoring of blood glucose levels.

Many types of insulin are available, including:

- Rapid-acting insulin
- Short-acting insulin
- Intermediate-acting insulin
- Long-acting insulin

Lifestyle Changes

Type 1 diabetes is a serious disease. Helping the child follow his or her diabetes treatment plan takes round-the-clock commitment and will initially require some significant lifestyle changes. Careful management of type 1 diabetes can reduce child's risk of serious - even life-threatening - complications.

- **Make a commitment to managing diabetes.** Take the medications as recommended. Learn about type 1 diabetes. Make healthy eating and physical activity.
- **Schedule physical and eye exams.**
- **Keep immunizations up to date.** High blood sugar can weaken immune system. A flu shot every year and the pneumonia vaccine, as well.
- **Pay attention to the feet.**
- **Keep blood pressure and cholesterol under control.**
- **Smoking:** Smoking increases risk of diabetes complications, including heart attack, stroke, nerve damage and kidney disease. So smoking should be prohibited.
- **Keep stress under control.**

Prevention:

Type 1 diabetes is not currently preventable. Some researchers believe it might be prevented at the latent autoimmune stage, before it starts destroying beta cells.

Reference:

- www.diabetes.org
- www.nhs.uk
- www.mayoclinic.org
- www.wikipedia.org

Test Yourself - 42

Correct Answers :

1.	a	2.	c	3.	d	4.	c	5.	c	6.	b

CONGRATULATIONS!

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FCPS (Obs & Gynae), Consultant
SOMCH Sylhet

Test Yourself - 43

1. The followings are true for "Superbug Manifestation" except:

a. Each year superbugs kill at least 23,000 people nationwide in USA.

b. Increasing use of antibiotics depletes the good microbes in the individual's gut.

c. The antibiotics kill everything including the resistant bacteria.

d. One of the recent superbugs to manifest came from the over use of the antibiotic class called Carbapenems.

2. All the followings are correct for "Postmenopausal Osteoporosis" except:

a. There are five phases to bone remodeling.

b. At menopause, there is an increased activation of remodeling sites due to reduction of estrogen hormone.

c. Women with low premenopausal estrogen levels are in less risk of developing osteoporosis.

d. In dual x-ray absorbtiometry(DXA), the radioisotope source is replaced by an x-ray source.

3. All the below are true for "Parkinson's Disease" except:

a. Dopamine agonists are commonly reserved for individuals more than 70 years of age.

b. MAO - B inhibitors are good choice as initial treatment for many patients.

c. Levodopa, dopamine agonists and anticholinergics each provide good benefit for tremor in about 50% - 60% of patients.

d. In clinical practice, the SSRIs are most commonly used medications to treat depression in Parkinson's disease.

4. All the followings are correct for "Postmenopausal Osteoporosis" except:

a. A total calcium intake of 1200 mg - 1500mg per day is recommended for all postmenopausal women.

b. Teriparatide is an antiresorptive agent that lowers risk of both vertebral and non-vertebral fractures.

c. Denosumab was the first biologic therapy approved to treat osteoporosis.

d. Vitamin D is essential for skeletal maintenance and enhancement of calcium absorption.

5. The followings are right for "Superbug Manifestation" except:

a. Multidrug resistant Pseudomonas aeruginosa mostly affects hospital patients.

b. Clostridium difficile most often affects the younger persons.

c. MRSA has become resistant to several powerful antibiotics.

d. Drug resistant tuberculosis has emerged over the years and some do not respond to many types of antibiotics.

6. All the followings are correct for "Parkinson's Disease" except:

a. Pimavanserin was approved in April, 2016 for treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

b. Anticholinergics are commonly used as symptomatic treatment of Parkinson's disease.

c. Dopamine agonists are less effective as monotherapy in early Parkinson's disease.

d. Cognitive behavioral therapy can help control impulse behaviors in Parkinson's disease.

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