Introduction to the pharmacology of the central nervous system (CNS) drugs

Introduction

Neurotransmitter (NT) (can be called as chemical transmitter or chemical messenger) is defined as any of a group of chemical agents are synthesized in presynaptic neurons and are released into synaptic cleft to rapidly stimulate or inhibit postsynaptic neurons, thus allowing impulses to be passed from one cell to the next throughout the nervous system. There are different types of CNS neurotransmitters, however; some of them were briefly discussed below:

1- Amino Acid Neurotransmitters

These compounds are present in high concentrations in the CNS and are extremely potent modifiers of neuronal excitability.

They are classified into two categories:

a- The acidic amino acid glutamate (Excitatory neurotransmitters, such as **glutamate**).

b- The neutral amino acids glycine and GABA (inhibitory neurotransmitters, such as **GABA and Glycine**).

2- Acetylcholine

Acetylcholine was the first compound to be identified pharmacologically as a transmitter in the CNS. Its action can affect cell bodies at all levels and it has excitatory and inhibitory effects depending on the receptor types that will bind with. For example, if it binds with M1 receptor, it will exhibit an excitatory effect. on the other hand, it will exhibit an inhibitory effect when it binds with M2 receptors.

3- Monoamine Neurotransmitters

These compounds are present in very small amounts in the CNS and they include the catecholamines (dopamine and norepinephrine) and 5-hydroxytryptamine (5-HT, serotonin).

A- Dopamine

Dopamine appears to be an inhibitory neurotransmitter and it plays an important role in controlling a wide range of body actions such as the regulation of motor functions. Five dopamine receptors have been identified, and they fall into two categories: D1-like (D1 and D5) and D2-like (D2, D3, D4). Dopamine is particularly important in relation to neuropharmacology, especially in Parkinson's disease and schizophrenia.

B- Norepinephrine

is an endogenous catecholamine exhibiting either excitatory or inhibitory effects depending on the receptor types that will bind with. For example, if it binds with α1 and β1 receptors, it will exhibit an excitatory effect. On the other hand, it will exhibit an inhibitory effect when it binds with receptors α2 and β2.

C- 5-hydroxytryptamine (5-HT, serotonin)

In most areas of the CNS, 5-HT has a strong inhibitory action, which is mediated by 5-HT1A receptors. 5-HT has been implicated in the regulation of virtually all brain functions, including perception, mood, anxiety, pain, sleep, appetite, temperature and neuroendocrine control.

There are other types of neurotransmitters such as Neuropeptides (such as opioid peptides, substance P and somatostatin), Nitric Oxide and Endocannabinoids {The primary psychoactive ingredient in cannabis is the Δ9- tetrahydrocannabinol}.

Sedative-Hypnotic Drugs:

The mean of the sedative-hypnotic class indicates that it can cause sedation (with concomitant relief of anxiety) or to encourage sleep (hypnosis). The most important groups of **these drugs are discussed and summarized below:**

1- BENZODIAZEPINES (BZ)

Benzodiazepines are widely used anxiolytic drugs because they are generally considered to be safer and more effective. Though BZs are commonly used, they are not necessarily the best choice for anxiety or insomnia as certain antidepressants with anxiolytic action, such as the selective serotonin reuptake inhibitors, are preferred in many cases, and nonbenzodiazepine hypnotics and antihistamines may be preferable for insomnia. (The commonly used BZs are Diazepam, Xanax and Lorazepam.)

Scientific name	Trade name
Alprazolam	XANAX
Chlordiazepoxide	LIBRIUM
Clonazepam	KLONOPIN
Clorazepate	TRANXENE
Diazepam	VALIUM, DIASTAT
Estazolam	
Flurazepam	DALMANE
Lorazepam	ATIVAN
Midazolam	VERSED
Oxazepam	
Quazepam	DORAL
Temazepam	RESTORIL
Triazolam	HALCION

Mechanism of action

The targets for BZs actions are the γ-aminobutyric acid (GABAA) receptors. [Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).] The GABAA receptors are composed of a combination of five α, β, and γ subunits that span the postsynaptic membrane (Figure 1). For each subunit, many subtypes exist (for example, there are six subtypes of the α subunit). Binding of GABA to its receptor triggers an opening of the central ion channel, allowing chloride through the pore (Figure 1). The influx of chloride ions causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials. BZs modulate GABA effects by binding to a specific, high-affinity site (distinct from the GABA-binding site) located at the interface of the α subunit and the γ subunit on the GABAA receptor (Figure 1). [Note: These binding sites are sometimes labelled "benzodiazepine (BZ) receptors." Common BZ receptor subtypes in the CNS are designated as BZ1 or BZ2 depending on whether the binding site includes an α1 or α2 subunit, respectively.] Benzodiazepines increase the frequency of channel openings produced by GABA. [Note: Binding of a benzodiazepine to its receptor site increases the affinity of GABA for the GABA binding site (and vice versa).] The clinical effects of the various BZs correlate well with the binding affinity of each drug for the GABA receptor–chloride ion channel complex.

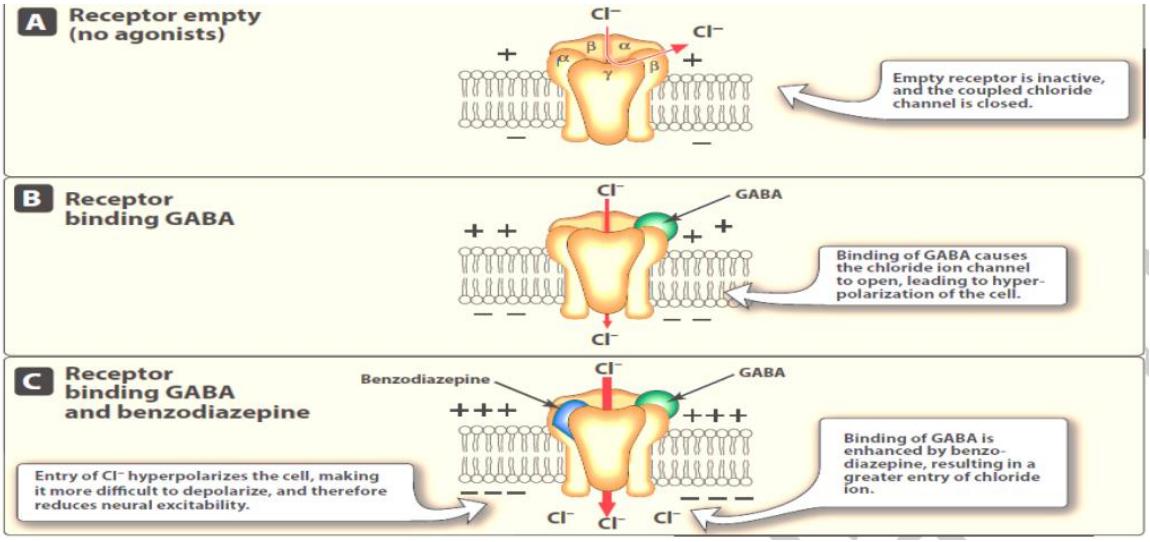

Figure 1: Schematic diagram of benzodiazepine–GABA–chloride ion channel complex. GABA = γ-aminobutyric acid.

Therapeutic uses

The individual BZs show small differences in their relative anxiolytic, anticonvulsant, and sedative properties. However, the duration of action varies widely among this group, and pharmacokinetic considerations are often important in choosing one BZs over another.

1. **Anxiety disorders:**
   - BZs are effective for the treatment of the different types of anxiety such as the anxiety symptoms secondary to panic disorder and obsessive–compulsive disorder, and extreme anxiety associated with phobias, such as fear of flying.
   - These drugs should be reserved for severe anxiety only and not used to manage the stress of everyday life. Because of their addiction potential, they should only be used for short periods of time.
   - The longer-acting agents, such as lorazepam, and diazepam, are often preferred in those patients with anxiety that may require prolonged treatment. The antianxiety effects of the BZs are less subject to tolerance than the sedative and hypnotic effects. [Note: Tolerance (that is, decreased responsiveness to repeated doses of the drug) occurs when used for more than 1 to 2 weeks.
   - Tolerance is associated with a decrease in GABA receptor density.
2. **Sleep disorders:** A few of the BZs are useful as hypnotic agents. These agents decrease the latency to sleep onset and increase stage II of non–rapid eye movement (REM) sleep.
3. **Amnesia**: The shorter-acting agents are often employed as premedication for anxiety-provoking and unpleasant procedures, such as endoscopy and dental procedures. They cause a form of conscious sedation, allowing the person to be receptive to instructions during these procedures.
4. **Seizures:**
   - Clonazepam is occasionally used as an adjunctive therapy for certain types of seizures, whereas lorazepam and diazepam are the drugs of choice in terminating status epilepticus.
   - Diazepam, lorazepam, and oxazepam are useful in the acute treatment of alcohol withdrawal and reduce the risk of withdrawal-related seizures.
5. **Muscular disorders:** Diazepam is useful in the treatment of skeletal muscle spasms.

Adverse effects

- Drowsiness and confusion are the most common side effects of the BZs. • Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile.
- Alcohol and other CNS depressants enhance the sedative–hypnotic effects of the benzodiazepines.
- A drug overdose of BZs is seldom lethal unless other central depressants, such as alcohol, are taken concurrently.

- To overcome the BZs overdose effect, BZ antagonist flumazenil (which is a GABA receptor antagonist) that can rapidly reverse the effects of benzodiazepines. The drug is available for intravenous (IV) administration only. As it has a short duration of action and a rapid onset, frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine.

2- BARBITURATES

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. Today, they have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance and physical dependence and are associated with very severe withdrawal symptoms. All barbiturates are controlled substances.

Mechanism of action

The sedative–hypnotic action of the barbiturates is due to their interaction with GABAA receptors, which enhances GABAergic transmission. The binding site of barbiturates on the GABA receptor is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings. This molecular action lead to decreased neuronal activity.

Therapeutic uses

1. **Anesthesia**: The ultra–short-acting barbiturates, such as thiopental, have been used intravenously to induce anesthesia but have largely been replaced by other agents.

2. **Anticonvulsant**: Phenobarbital has specific anticonvulsant activity. So, it can be used in long-term management of tonic–clonic seizures. However, phenobarbital can depress cognitive development in children and decrease cognitive performance in adults, and it should be used only if other therapies have failed. Similarly, phenobarbital may be used for the treatment of refractory status epilepticus.

3. **Sedative/hypnotic**: Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. The use of barbiturates for insomnia is no longer generally accepted because of the adverse effects and potential for tolerance. Butalbital is commonly used in combination products (with acetaminophen and caffeine or aspirin and caffeine) as a sedative to assist in the management of migraine headaches.

Adverse effects

- Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness. The CNS depressant effects of barbiturates synergize with those of ethanol.

• Hypnotic doses of barbiturates produce a drug "hangover" that may lead to impaired ability to function normally for many hours after waking.

• Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are metabolized by the CYP450 system.

• Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates and can result in death.

3- OTHER HYPNOTIC AGENTS

a- Zolpidem

- The hypnotic zolpidem is not structurally related to benzodiazepines, but it selectively binds to the benzodiazepine receptor subtype BZ1. Zolpidem has no anticonvulsant or muscle-relaxing properties.
- It shows few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance occurs with prolonged use. Zolpidem is rapidly absorbed from the gastrointestinal (GI) tract, and it has a rapid onset of action and it can provide a hypnotic effect for approximately 5 hours. [Note: A lingual spray and an extended-release formulation are also available. A sublingual tablet formulation may be used for middle-of-the-night awakening.]
- Adverse effects of zolpidem include nightmares, agitation, headache, GI upset, dizziness, and daytime drowsiness.
- Unlike the benzodiazepines, at usual hypnotic doses, the nonbenzodiazepine drugs such as zolpidem, zaleplon, and eszopiclone, do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics. This may be due to their relative selectivity for the BZ1 receptor. All the last three mentioned agents are controlled substances.

b- Antihistamines

Some antihistamines with sedating properties, such as diphenhydramine, are effective in treating mild types of situational insomnia. However, they have undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines. Some sedative antihistamines are marketed in numerous over-thecounter products.

Antiseizure drugs (Drugs for Epilepsy)

Introduction

Epilepsy is not a single entity but an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons. This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behaviour, and distorted perceptions that are of limited duration but recur if untreated. Epilepsy can be due to an underlying genetic, structural, or metabolic cause or an unknown cause.

CLASSIFICATION OF SEIZURES

It is important to correctly classify seizures to determine appropriate treatment. Seizures have been classified into two broad groups: focal and generalized.

A- Focal

Focal seizures involve only a portion of the brain. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain. Focal seizures may progress to become generalized tonic–clonic seizures.

1- **Simple partial**: The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. The patient may also show sensory distortions. This activity may spread. Simple partial seizures may occur at any age.

2- **Complex partial**: These seizures exhibit complex sensory hallucinations and mental distortion. Motor dysfunction may involve chewing movements, diarrhea, and/or urination. Consciousness is altered. Simple partial seizure activity may spread to become complex and then spread to a secondarily generalized convulsion. Complex partial seizures may occur at any age.

B- Generalized

Generalized seizures may begin locally and then progress to include abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or nonconvulsive, and the patient usually has an immediate loss of consciousness.

1. **Tonic–clonic**: These seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The

seizure may be followed by a period of confusion and exhaustion due to the depletion of glucose and energy stores.

2. **Absence**: These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye-blinking, which lasts for 3 to 5 seconds.
3. **Myoclonic**: These seizures consist of short episodes of muscle contractions that may recur for several minutes. They generally occur after wakening and exhibit as brief jerks of the limbs. Myoclonic seizures occur at any age but usually begin around puberty or early adulthood.
4. **Clonic**: These seizures consist of short episodes of muscle contractions that may closely resemble myoclonic seizures. Consciousness is more impaired with clonic seizures as compared to myoclonic.
5. **Tonic**: These seizures involve increased tone in the extension muscles and are generally less than 60 seconds long.
6. **Atonic**: These seizures are also known as drop attacks and are characterized by a sudden loss of muscle tone.

Mechanism of action of antiepilepsy medications

Drugs reduce seizures through such mechanisms as blocking voltage-gated channels (Na+ or Ca2+), enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses and interfering with excitatory glutamate transmission. Some antiepilepsy medications appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined. Antiepilepsy medications suppress seizures but do not "cure" or "prevent" epilepsy.

ANTIEPILEPSY MEDICATIONS

1- Benzodiazepines (BZs)

Benzodiazepines bind to GABA inhibitory receptors to reduce firing rate. Most BZs are reserved for emergency or acute seizure treatment due to tolerance. Diazepam is also available for rectal administration to avoid or interrupt prolonged generalized tonic–clonic seizures or clusters when oral administration is not possible.

2- Carbamazepine (Tegretol)

Carbamazepine blocks sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread. Carbamazepine is effective for treatment of focal seizures and, additionally generalized tonic–clonic seizures.

3- GABAPENTIN & PREGABALIN

Gabapentin and pregabalin, known as "gabapentinoids," are amino acid-like molecules that were originally synthesized as analogs of GABA but are now known not to act through GABA mechanisms. So, they do not act at GABA receptors, enhance GABA actions or convert to GABA. Their precise mechanism of action is not known. They are used in the treatment of focal seizures and various nonepilepsy indications, such as neuropathic pain, restless legs syndrome, and anxiety disorders.

4- Phenobarbital and primidone

- The primary mechanism of action of phenobarbital is enhancement of the inhibitory effects of GABA-mediated neurons. Primidone is metabolized to phenobarbital (major) and phenylethylmalonamide, both with anticonvulsant activity. Phenobarbital is used primarily in the treatment of status epilepticus when other agents fail.
- Phenobarbital is no longer a first choice in the developed world because of its sedative properties and many drug interactions. It is still useful for neonatal seizures
- In comparison with anesthetic barbiturates such as pentobarbital, phenobarbital is preferred in the chronic treatment of epilepsy because it is less sedative at antiseizure doses.

5- Phenytoin and fosphenytoin

Phenytoin blocks voltage-gated sodium channels. It is effective for treatment of focal and generalized tonic–clonic seizures and in the treatment of status epilepticus. **Gingival hyperplasia** may cause the gums to grow over the teeth. Long-term use may lead to development of peripheral neuropathies and osteoporosis. Although phenytoin is advantageous due to its low cost, the actual cost of therapy may be much higher, considering the potential for serious toxicity and adverse effects like nystagmus and ataxia.

Fosphenytoin is a prodrug that is rapidly converted to phenytoin in the blood within minutes. Whereas fosphenytoin may be administered intramuscularly (IM), phenytoin sodium should never be given IM, as it causes tissue damage and necrosis. Fosphenytoin is the drug of choice and standard of care for IV and IM administration of phenytoin. Because of sound-alike and look-alike trade names, there is a risk for prescribing errors.

STATUS EPILEPTICUS:

In status epilepticus, two or more seizures occur without recovery of full consciousness in between episodes. These may be focal or primary generalized, convulsive or nonconvulsive. Status epilepticus is life threatening and requires emergency treatment usually consisting of

administration of a fast-acting medication such as a benzodiazepine, followed by a slower-acting medication such as phenytoin.

ANTIDEPRESSANT DRUGS

Introduction

The symptoms of **depression** are feelings of sadness and hopelessness, as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts.

Mania is characterized by the opposite behaviour: enthusiasm, anger, rapid thought and speech patterns, extreme self-confidence, and impaired judgment.

GENERAL MECHANISM OF ANTIDEPRESSANT DRUGS

Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin (5-HT) in the brain. This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain. Conversely, the theory proposes that mania is caused by an overproduction of these neurotransmitters. However, the biogenic amine theory of depression and mania is overly simplistic. It fails to explain the pharmacological effects of any of the antidepressant and antimania drugs on neurotransmission, which often occur immediately; however, the time course for a therapeutic response occurs over several weeks. This suggests that decreased reuptake of neurotransmitters is only an initial effect of the drugs, which may not be directly responsible for the antidepressant effects.

1- SELECTIVE SEROTONIN REUPTAKE INHIBITORS

• The selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressant drugs that specifically inhibit serotonin reuptake. The antidepressant effect typically takes at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more.

• Because they have different adverse effects and are relatively safe even in overdose, the SSRIs have largely replaced TCAs (tricyclic antidepressant drugs) and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression.

• The SSRIs include fluoxetine (the prototypic drug), citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline.

• The primary indication for SSRIs is depression, for which they are as effective as the TCAs. A number of other psychiatric disorders also respond favourably to SSRIs such as obsessive–compulsive disorder and panic disorder.

• Although the SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs, some side effects are recorded for SSRIs such as

headache, sweating, anxiety and agitation, gastrointestinal (GI) effects (nausea, vomiting, diarrhea), weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances (like insomnia).

• Seizures are the possible side effects because all antidepressants may lower the seizure threshold.

• Moreover, All SSRIs have the potential to cause serotonin syndrome, especially when used in the presence of a MAOI or other highly serotonergic drug. Serotonin syndrome is a potentially life-threatening syndrome that is precipitated by the use of serotonergic drugs and overactivation of both the peripheral and central serotonin receptors.

• Serotonin syndrome can occur via the therapeutic use of serotonergic drugs alone, an intentional overdose of serotonergic drugs, or classically, as a result of a complex drug interaction between two serotonergic drugs that work by different mechanisms. Serotonin syndrome may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs.

• **Discontinuation syndrome**: All of the SSRIs have the potential to cause a discontinuation syndrome after their abrupt withdrawal. Possible signs and symptoms of SSRI discontinuation syndrome include headache and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern.

2- SEROTONIN/NOREPINEPHRINE (NE) REUPTAKE INHIBITORS (SNRIs)

• SNRIs are a group of antidepressant drugs that inhibit the NE and serotonin reuptake.

• It includes venlafaxine, desvenlafaxine, levomilnacipran, and duloxetine. • These agents may be effective in treating depression in patients in whom SSRIs are ineffective.

• Furthermore, depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineffective. This pain is, in part, modulated by serotonin and norepinephrine pathways in the central nervous system (CNS).

• Both SNRIs and the TCAs, with their dual inhibition of both serotonin and norepinephrine reuptake, are sometimes effective in relieving pain associated with diabetic peripheral neuropathy and low back pain.

• The SNRIs, unlike the TCAs, have little activity at α-adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the TCAs. The SNRIs may precipitate a discontinuation syndrome if treatment is abruptly stopped.

3- TRICYCLIC ANTIDEPRESSANTS

The TCAs block NE and serotonin reuptake into the presynaptic neuron. The TCAs include the tertiary amines imipramine (the prototype drug), amitriptyline, doxepin, and trimipramine and the secondary amines desipramine and nortriptyline. Patients who do not respond to one TCA may benefit from a different drug in this group.

Mechanism of action

1. Inhibition of neurotransmitter reuptake: TCAs and amoxapine (which is related "tetracyclic" antidepressant agents and is commonly included in the general class of TCAs.) are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals.

2. Blocking of receptors: TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors. It is not known if any of these actions produce the therapeutic benefit of the TCAs. However, actions at these receptors are likely responsible for many of their adverse effects.

Therapeutic uses

The TCAs are effective in treating moderate to severe depression. Some patients with panic disorder also respond to TCAs.

Imipramine has been used to control bed-wetting in children older than 6 years of age; however, it has largely been replaced by desmopressin and nonpharmacologic treatments (enuresis alarms).

The TCAs, particularly amitriptyline, have been used to help prevent migraine headache and treat chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of pain is unclear.

Adverse effects

- Blockade of muscarinic receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia and constipation.

- These agents affect cardiac conduction and may precipitate life-threatening arrhythmias in an overdose situation.

- The TCAs also block α-adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia. Imipramine is the most likely, and nortriptyline the least likely, to cause orthostatic hypotension.

• Sedation may be prominent, especially during the first several weeks of treatment, and is related to the ability of these drugs to block histamine H1 receptors.

• Weight gain is a common adverse effect of the TCAs.

• TCAs (like all antidepressants) should be used with caution in patients with bipolar disorder, even during their depressed state, because antidepressants may cause a switch to manic behaviour.

• The TCAs have a narrow therapeutic index (for example, five- to six-fold the maximal daily dose of imipramine can be lethal).

4- MONOAMINE OXIDASE INHIBITORS

• Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues. In the neuron, MAO functions as a "safety valve" to oxidatively deaminate and inactivate any excess neurotransmitters (for example, norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest.

• The MAOIs may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitters to escape degradation and, therefore, to accumulate within the presynaptic neuron and leak into the synaptic space.

• The four MAOIs currently available for treatment of depression include phenelzine, tranylcypromine, isocarboxazid, and selegiline.

• Selegiline is also used for the treatment of Parkinson's disease. It is the only antidepressant available in a transdermal delivery system.

• Use of MAOIs is limited due to the complicated dietary restrictions required while taking these agents.

• The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs and SSRIs or who experience strong anxiety.

• A special subcategory of depression, called atypical depression, may respond preferentially to MAOIs.

• Because of their risk for drug– drug and drug–food interactions, the MAOIs are considered last-line agents in many treatment settings.

• Enzyme regeneration, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a

minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and the initiation of another antidepressant from any other class.

Adverse effects

- Severe and often unpredictable side effects, due to drug–food and drug–drug interactions, limit the widespread use of MAOIs.
- For example, tyramine, which is contained in foods, such as aged cheeses and meats, and chicken liver is normally inactivated by MAO in the gut. Individuals receiving a MAOI are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in a hypertensive crisis, with signs and symptoms such as headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke.
- Patients must, therefore, be educated to avoid tyramine-containing foods.
- Phentolamine and prazosin are helpful in the management of tyramineinduced hypertension.
- Other possible side effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation.
- Due to the risk of serotonin syndrome, the use of MAOIs with other antidepressants is contraindicated. For example, SSRIs should not be coadministered with MAOIs.

ATYPICAL ANTIDEPRESSANTS

The atypical antidepressants are a mixed group of agents that have actions at several different sites. **This group includes:**

A. Bupropion

Bupropion is a weak dopamine and norepinephrine reuptake inhibitor that is used to alleviate the symptoms of depression. Bupropion is also useful for decreasing cravings and attenuating withdrawal symptoms of nicotine in patients trying to quit smoking. Side effects may include dry mouth, sweating, nervousness, tremor, and a dose dependent increased risk for seizures.

B. Mirtazapine

Mirtazapine enhances serotonin and NE neurotransmission by serving as an antagonist at presynaptic α2 receptors. Additionally, some of the antidepressant activity may be related to antagonism at 5-HT2 receptors. It is sedating because of its potent antihistaminic activity, but it does not cause the antimuscarinic side effects of the TCAs, or interfere with sexual function like the SSRIs. Mirtazapine is markedly sedating, which may be an advantage in depressed patients having difficulty sleeping.

Antipsychotic Drugs

Introduction

- The antipsychotic drugs (also called neuroleptics or major tranquilizers) are used primarily to treat schizophrenia, but they are also effective in other psychotic and manic states.

- Antipsychotic drugs are not curative and do not eliminate chronic thought disorders, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

- Schizophrenia is a type of chronic psychosis characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances.

ANTIPSYCHOTIC DRUGS

The antipsychotic drugs are divided into first- and second-generation agents. This classification does not indicate clinical effectiveness of the drugs, but rather specifies affinity for the dopamine D2 receptor, which, in turn, may influence the adverse effect profile of the drug.

A. First-generation antipsychotics

The first-generation antipsychotic drugs (also called conventional, typical, or traditional antipsychotics) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine D2 receptors. Firstgeneration antipsychotics are more likely to be associated with movement disorders known as extrapyramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuroreceptors, such as haloperidol. Movement disorders are less likely with medications that bind weakly, such as chlorpromazine. No one drug is clinically more effective than another.

C- Second-generation antipsychotic drugs

- The second-generation antipsychotic drugs (also called “atypical” antipsychotics) have a lower incidence of EPS than the first-generation agents but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain. The second- generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine and, perhaps, other receptors.

- **Drug selection**: Second-generation agents are generally used as first-line therapy for schizophrenia to minimize the risk of debilitating EPS associated with the first-generation drugs that act primarily at the dopamine D2 receptor.

• **Refractory patients**: Approximately 10% to 20% of patients with schizophrenia have an insufficient response to all first- and second-generation antipsychotics. For these patients, clozapine has shown to be an effective antipsychotic with a minimal risk of EPS. However, its clinical use is limited to refractory patients because of serious adverse effects. Clozapine can produce bone marrow suppression, seizures, and cardiovascular side effects.

Mechanism of action

1. Dopamine antagonism: All of the first-generation and most of the secondgeneration antipsychotic drugs block D2 dopamine receptors in the brain and the periphery.

2. Serotonin receptor–blocking activity: Most of the second-generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT2A receptors.

a. Clozapine has high affinity for D1, D4, 5-HT2, muscarinic, and αadrenergic receptors, but it is also a weak dopamine D2 receptor antagonist.

b. Risperidone and olanzapine blocks 5-HT2A receptors to a greater extent than it does D2 receptors.

c. Quetiapine blocks D2 receptors more potently than 5-HT2A receptors but is relatively weak at blocking either receptor. Its low risk for EPS may also be related to the relatively short period of time it binds to the D2 receptor.

Actions

The clinical effects of antipsychotic drugs appear to reflect a blockade at dopamine and/or serotonin receptors. However, many of these agents also block cholinergic, adrenergic, and histaminergic receptors. It is unknown what role, if any, these actions have in alleviating the symptoms of psychosis. However, the undesirable side effects of antipsychotic drugs often result from pharmacological actions at these other receptors.

1. **Antipsychotic effects:** All antipsychotic drugs can reduce hallucinations and delusions associated with schizophrenia (known as “positive” symptoms) by blocking D2 receptors in the brain. The “negative” symptoms, such as blunted affect, apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particularly with the first-generation antipsychotics. Many second-generation agents, such as clozapine, can ameliorate the negative symptoms to some extent.

2. **Extrapyramidal effects**: Dystonias (sustained contraction of muscles leading to twisting, distorted postures), Parkinson-like symptoms, akathisia (motor restlessness), and tardive dyskinesia (involuntary movements, usually of the tongue, lips, neck, trunk, and limbs) can

occur with both acute and chronic treatment. Blockade of dopamine receptors in the nigrostriatal pathway probably causes these unwanted movement symptoms. The second-generation antipsychotics exhibit a lower incidence of EPS.

3. **Antiemetic effects:** Most of the antipsychotic drugs have antiemetic effects that are mediated by blocking D2 receptors of the chemoreceptor trigger zone of the medulla.

4. **Anticholinergic effects:** Some of the antipsychotics, particularly thioridazine, chlorpromazine, clozapine, and olanzapine, produce anticholinergic effects. These effects include blurred vision, dry mouth (the exception is clozapine, which increases salivation), confusion, and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention.

5. **Other effects:** Blockade of α-adrenergic receptors causes orthostatic hypotension and light-headedness. The antipsychotics also alter temperature-regulating mechanisms and can produce poikilothermia (condition in which body temperature varies with the environment).

Therapeutic uses

1. **Treatment of schizophrenia:** The antipsychotics are considered the only efficacious pharmacological treatment for schizophrenia. The first-generation antipsychotics are most effective in treating positive symptoms of schizophrenia. The atypical antipsychotics with 5-HT2A receptor–blocking activity may be effective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms of schizophrenia.

2. **Prevention of nausea and vomiting:** The older antipsychotics (most commonly, prochlorperazine) are useful in the treatment of drug-induced nausea.

3. **Other uses:**

- The antipsychotic drugs can be used as tranquilizers to manage agitated and disruptive behaviour secondary to other disorders.
- Chlorpromazine is used to treat intractable hiccups.
- Risperidone and aripiprazole are approved for the management of disruptive behaviour and irritability secondary to autism.

Adverse effects

Adverse effects of the antipsychotic drugs can occur in practically all patients and are significant in about 80%.

1- **Extrapyramidal effects:**

The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects. The appearance of the movement disorders is generally time and dose dependent, with dystonias occurring within a few hours to days of treatment, followed by akathisias occurring within days to weeks.

Parkinson like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment.

If **cholinergic** activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized. This can be achieved by administration of an anticholinergic drug, such as benztropine.

2- **Tardive dyskinesia:** Long-term treatment with antipsychotics can cause this motor disorder. Patients display involuntary movements, including bilateral and facial jaw movements and "fly-catching" motions of the tongue. A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy.

Tardive dyskinesia is postulated to result from an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine receptor blockade. This makes the neuron supersensitive to the actions of dopamine, and it allows the dopaminergic input to this structure to overpower the cholinergic input, causing excess movement in the patient.

3- **Neuroleptic malignant syndrome:** This potentially fatal reaction to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia. Treatment necessitates discontinuation of the antipsychotic agent and supportive therapy.

4- **Other effects:**

- Drowsiness occurs due to CNS depression and antihistaminic effects, usually during the first few weeks of treatment.
- Confusion sometimes results.
- Those antipsychotic agents with potent antimuscarinic activity (like thioridazine, chlorpromazine) often produce dry mouth, urinary retention, constipation, and loss of visual accommodation.
- Others may block α-adrenergic receptors (like chlorpromazine), resulting in lowered blood pressure and orthostatic hypotension.
- The antipsychotics depress the hypothalamus, affecting thermoregulation and causing amenorrhea, gynecomastia, infertility, and erectile dysfunction.

- Glucose and lipid profiles should be monitored in patients taking antipsychotics due to the potential for the second-generation agents to increase these laboratory parameters and the possible exacerbation of preexisting diabetes or hyperlipidemia.
- Some antipsychotics have been associated with mild to significant QT prolongation.

Cautions and contraindications:

All antipsychotics may lower the seizure threshold and should be used cautiously in patients with seizure disorders or those with an increased risk for seizures, such as withdrawal from alcohol.

Maintenance treatment

Patients who have had two or more psychotic episodes secondary to schizophrenia should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy. Low doses of antipsychotic drugs are not as effective as higherdose maintenance therapy in preventing relapse. The rate of relapse may be lower with second-generation drugs.

References:

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2- Whalen, K., 2019. ***Lippincott illustrated reviews: pharmacology***. Lippincott Williams & Wilkins.