Pharmacology One.

< CNS Pharmacology Summary >

Student: **Ahmed J. Skaik**

Lecturer: **Dr. Rasha Bseiso**

Semester: **Second Semester of the year 2021/2022**

alazharpharmacy.com

* pharmacology I :-

·lec (13) : **CNS**

*chapter (8) : Drugs for Neurodegenerative Diseases

Neurodegenerative Disease /

~~Drugs~~ Diseases Related to complete loss of Neurones,
in which they can't be restored.
Symptoms appear after losing large Number of Neurones
cause the left Neurones will Try to compensate the
loss.

the loss of specific Types of Neurones

---

any drug works centrally will effect the Neuro-
-Transmission.

they work presynaptically " بتشتغل على مستوى
اول ما بيتم تصنيعه ، لما يخزنه
بالـ vesicle ، لما يحرره
Release ، في الأدوية قادرة
تمنع كل هالعمليات
أو تمنع الـ storage أو حتى الـ Release .. "

later, as any other drug it can Block the post

Synaptic Rec.

the peripheral Nervous System Drugs Mostly
Works Parasympathically.
Very Rare Presympathically.

examples of Neurodegenerative diseases:-

- Multiple Sclerosis التصلب المتعدد
  - Multipe => More than one area is damaged at the same time
  - Sclerosis => Rigidity, Muscles lose their flexibility, less to Myelin Sheet in the level of CNS

  Rare, but very Serious.

- parkenson's, Alzhimer's Disease:-
  progressive loss of selective Neurches family -cholenergic Neurches-, -Adrenergic Neurches-
  these but undergo progressive loss,
  if started, will continue..
  but it different Rates BTW patients

it will cause disorder in Movement, Cognition or both.

the disease related to the specific Neurons lost.

↳ Movement problems ⇒ parkenson's

↳ Cognetion problems ⇒ Alzehimer's

*Neurotransmission in the CNS :-

CNS, PNS similar in the basic function

So .. study the difference

↳ Neural circuitry

Much More complex compare w the in the ~~A~~NS.

↳ Presynaptic - postsynaptic - post

But here we can say it as simple

↳ No. of synapses in CNS is Much greater "Spaces BW Neurones"

Cause No. of Neurones is greater, so Neurotransmission is faster,

↳ inhibitory Neurotransmitters "powerful Network of inhibitory Neurotransmitters"

in ANS ⇒ Ach, NE Both excitatory
inhibitory for CNS

CNS ⇒ stimulatory, inhibitory ⇒ Modulation
Se Communicate ⇒ Multiple Neurotransmitters
GABA, Glutamate, Dopamin...

↳ Rec. of CNS Most of them ~~of~~ of the all
of them are ligand gated ion channel
ionotropic.
compare ⇒ ANS Most of them are
Metabotropic.
only Nicotinic in NMJ where ionic

↳ CNS ⇒ Neurotransmitter Activate its Rec. but
the Result of the Activation May
be inhibitory depending on the
Neurotransmitter.
ex: GABA / glutamate Both will
Activate their own Rec. polarized
Due to glutamate ⇒ excitation Na^+
GABA ⇒ inhibit Cl^- hyperpolarization

Describing Depolarization / Repolarization / Hyperpolarize

EPSP \ IPSP ⇒ Inhibitory postsynaptic resp.

↳ Excitatory postsynaptic potent.

Associated w Na+ channel

for EPSP to occur, there must be Number of stimulating Neurons Reached to Space level to Reach Threshold!

Since it's Complex circuit, Many Neurotransmitters will be secreted at the same Time working on their Rec. causing IPSP, EPSP ⇒ overall Action is Summation of All EPSP, IPSP

*Parkinson's Disease :-

it's a progressive Neurodegenerative disorder of the Neuromuscular System

"Neurodegenerative Neuromuscular Disorders"

ذلك الاضطراب يؤثر على
العضلات .

it's a disease of elderly, but may happen to younger people "Rare".

the disease Related to Basal ganglia are The Regions in the Basal ganglia
Black substance = L→ Substantia Nigra
L→ Neostriatum
cerebellum جسم المخ

it's Near to cerebellum cause it's Responsible for balance,
while the Basal ganglia ⇒ Coordination, initiations of Movement
مركة الجسم اثناء الحركة

output fibers of Basal ganglia is Mostly Inhibitory
اي تثبيط على الزيادة

the problem = parkinson is Problem in the basal ganglia, Mostly Problem in Substantia Nigra for idiopathic Reason.
or Might be Secondary due to Cause effected the Substantia Nigra or the Basal ganglia in general

Characterised by

- Tremors
- Rigidity
- Bradykinesia
- Postural instability

Stiffness in Muscles

Most parkenson's patients die due to depression!

Fig 8.11

Neostriatum, Substantia Nigra specially the Substantia are part of system in Brain inside the Basal ganglia called the Extrapyramidal system.

- If drug have Extrapyramidal side effect it effects the Substantia, Neostriatum directly.

Substantia Nigra is the Main Area in Basal ganglia Responsable for Dopamin secretion

Dopamen in Neostriatum is inhebetory

At the same time Nonstriatum sends to the substantia ⇒ GABA which is also inhibitory

the Nonstriatum inside it there is Ach which is excitatory.
being working ⊃ levels of Ach, signals of Neurons is to. Much stimulatory, inhibitory ..
& left alone "over"

Normally two inhibitory pathways sending each the inhibitory Neurons.

So..
in the system
↳ Ach
↳ Dopamin
~~↳ GABA~~ 없음 →

GABA is inhibitory Neurotransmitter so since Nonstriatum sends it.
it keeps substantia Nogra in Balance State

substantia Nogra is dopaminergic system
its originally causing Activity →

There is Activity, but ⇒ the Muscle is tonic and sustaining instead of giving high Activity by Ach, Dopamin will Reduce the partial agents ∝ D

in case of parkinson ⇒ less of Dopamergic Neurones in substantia Nigra, Leading the tonic Substance Motor Inhibition effect.
Now Ach will Directly effected
So Neostriatum No left in Ach controlling the Motor Inhibition.

Leading inhibitory effect of Dopamin while ⇒ over activity of cholinergic Neurones ∈ idiopathic parkinson

Secondary parkinsonism is secondary To the use of other drugs such as phenothiazines, haloperidol

that are Antipsychotics "Dopamine Antagonist"

→ losing Dopamine!

→ chronic use ⇒ (E.P.S.E) → or the extra pyramidal system

Ach being stimulatory Neurotransmitter, it's Role in the parkinson signs like tremors, Muscle Rigidity → "Ach ⇒ control"

on the other hand → brady kinesis (↓ Dopamine)

Strategy of ↑↑↑ is

↳ ↓ Ach

↳ ↑ Dopamine

Extra pyramidal side effects

* pharmacology 4 :.

• lec (1M) :-

* Drugs used in parkinson's Disease :-

اول حاجه هنحفظ اهم 2 ماسكين بس

↳ Levodopa and Carbidopa

↳ first line for parkinson, بتوصل Dopamin
works as precursor of dopamin,
Must enter BBB then turn
it self into dopamin

Carbidopa doesn't have direct
effect Therapeutically, but
given cause it inhibits an enzyme
Breack down levodopa called "
Dopamin decarboxylase" Break it
Down in periphery.

Dopa ⟹ NE in Adrenergic Neurone (r-Dopamin)
↳ ⟹ Dopamin in Dopaminergic Neurones.

ال... levodopa مش هتعمل اثر الا لو في
Dopaminergic Neurones تقريبا ٥٠٪ منها
انا جبت levodopa عشان تنشط.

in the early stages of disease, Response to the drug is consistance,
the more develop the disease stage the less the effect of the given does
"wearing off phenomena" the effect of drug disappear.
cause more Neurones die ..

*Why to give levodopa not Dopamin?!
Dopamin is a Catecholamin so, containing the OH's on the benzen Ring,
won't penetrate the CNS.
but levodopa penetrate CNS, then form dopamin.

*U-S increase in the dose was noticed ~~when given~~ in levodopa when Adrenesteres w carbodopa.

also if not giving carbodopa, the normal dose of levodopa will cause side effect on the periphry ⟹ Dopamin will work as Adrenergic Agonist ⟹ Tachycardia, hypertention
Dopaminergic, Adrenergic Rec ⟹ Tachycard.
↳ Vasodilatation

use causes Nausia, Vomiting, Cardiac Arrythmia initiated due to overactivating of heart.

So giving Carbidopa, I avoid all that

- Therapeutic uses:-
  - Later impairment of symptoms in in 2/3 of the total patients.
  - Symptoms decrease in the first 2-3 years, start to decline after the 5th year where wearing-off phenomena appear, due to the loss of dopaminergic Neurones

  though, I can't suddenly stop it even if want to replace it to ~~stress~~ something else.

- Adverse effects:-
  Mostly due to it's effect in Adrenergic, Dopaminergic Neurones
  - ↳ heart → Tachycardia, Arrythmia, hypertension.

↳ GIT
Nausia, Vomiting

↳ Eye
Mydriasis "Adrenergic α-Rec"

↳ Saliva, urin
Brown color, due to oxidation.

These are side effects of levodopa Breakdown in the periphery not the levodopa it self.

Now levodopa it self after turn into dopamin in the CNS.

↳ Confusion.

↳ Auditory, visual hallucinations

↳ psychosis, depression, Anxiety

Due to over Activity of dopamin,
& Don't know what parts will it
take
↳ inhibitory
↳ Activation
but these in chronic use, Most certainly

Metabolic changes.

Dyskinesia is the most famous side effect
Due to effects on the CNS.

- Bradykinesia ⇒ بطء الحركة
- involuntary, uncontrolled movements حركات لا إرادية

- MAO inhibitors
  The work selectivity on the MAO
  - Selegiline,
  - Rasagiline

MAO Breaks Down Dopamin, NE, Seretonin..
Most of Catecholamines.

MAO
- MAO-A ⇒ Non-Selective "for all"
- MAO-B ⇒ Mostly Dopamin

These drugs of MAO inhebitors are Selective
for MAO-B.
So Dopamin levels in Brain Stay High
May used alone or along side w levodopa

So Management of symptoms for longer time

Selectivity of MAO-B in these drugs depends on the dose.
the higher the dose the less the selectivity

A, B ⇒ [illegible] Selectivity (M-)

Due to that ⇒ Risk of hypertensive crises.

as long as I'm committed to the therapeutic Dose the Risk is low.

- Selegiline after given, it Breaks down Amphetamine, Methamphetamine
  to Drugs of Abuse.
  So using it May lead to dependance
- Rasagiline Doesn't, as potency 5 times higher than Selegiline
  But it's irreversible ⇒ [illegible]

[illegible] MAO [illegible]

Bye Bye cells

- COMT inhibitors

They can prevent the Break Down of levo-Dopa, but in pathway) Doesn't Relate to turn into dopamin.

- Entacapone — More used)
- Tolcapone — limited due to hepatic Toxicity).

They are selective, Reversible in inhebiting the COMT enzymes

Fig 8,7

levodopa can be Broken Down in the periphy by different pathways.

- decarboxylation ⇒ Sr Levels Dopamin in periphy ⇒ Problems

- Break down by COMT to inactive Metabolite 3-oMethyldopa that doesn't have any effect but Competes w levodopa in the intery to BBB

Solution:-

Carbidopa to inhibit DDC pathway

Entacapone to inhibit the second one

So ...

all levodopa pass CNS.

COMT inhibitors mostly given along with levodopa. بس مش ملزم استخدمها لحالها

Cause it works on prevent it turning to 3-O-Methyl dopa

The wearing-off phenomena will be altered.

· Adverse effects:-

Since I only use it in people who take levodopa, carbidopa the problems are related to that. "extra Dopamine"

+ hepatotoxicity for Tolcapone

Dopamine Receptor Agonists

- Ergot derivatives
  - Bromocriptine
- Nonergot derivatives
  - Apomorphine

They all will work as Dopamin Rec. Agonist,
So there Must be enough Rec. available & I see effect.

Bromocriptin can be given alone without levodopa.
will give similar effect to dopamin it acts / works like it Bind to dopamin Rec.
the problem of it, it will cause Mental conditions, psychiatric issues, Maybe psycosis.

I use it one to benefit - Risk Ratio.
though I can't use it w the same does for people w Blood vessles, heart issues cause it will worser the case

Chronic use causes fibrosis of the lung & retroperitoneal space. حواليه المدة
used specifically → people can't take levodopa, carbidopa as dyskinesia
or people take levodopa I give small doses of this drug to enhance things
it won't give the same side effects

[illegible]
[illegible]

when giving any of these drugs, they can give longer duration of action, efficacy more than that → levodopa
if someone suffers fluctuations in presence of levodopa

[illegible]
levodopa [illegible]

. they are effective in parkinsonism patients who have complicated disease → motor fluctuations, dyskinesia.

they are completely ineffective so severe didn't Response to levodopa.

1. Dopamine agonist Rec.

Dyskinesia Risk ↓ those drugs is so low causes vasospasm (8.3)

- Apomorphine
injection, Transdermal ⇒ Not orally
only in Advanced cases Adjuvant
to dopamine agonists taken orally.

used in Acute Management of "off-phenomenon"
hypomotility ~~hypomotility~~ hypomobility
Bradykinesia

- in early patients I can use these because they will delay the Need to use levodopa which is full of problems.
or in More Advanced cases I use less doses of levodopa to Avoid Side effects

Adverse effects as Mentioned, but not Discussed

The following drugs are used as Adjuvant for I → U.
Not as commonly used.

↳ **Amantadine**
it's An Antiviral drug used for influenza
they have effects on parkinson ∵ it
can penetrate BBB.
↑ Dopamin secretion,
↓ Activity of cholinergic Rec.,
inhibit glutamate Rec. called "NMDA"

. NMDA هي الـ glutamate الـ

but the Adverse effects on CNS is very high:
↳ Confusion
↳ Restlessness
↳ Hallucination
↳ Orthostatic HTN
↳ Urinary Retention ⇒ Anti-cholinergic effect
↳ Edema

The Main problem is Tolerance.

- Antimuscarinic Agents
  - Benzotropin
  - Trihexyphenidyl
  - Procyclidine
  - biperiden

Block cholinergic Neurones, they Reduce the Release BIW Ach, Depress its Stimulus Nigra, Neostriatum.

I can't use it alone, along side w levodopa

Adverse effects Dry Mouth xerostomia, memory Retention ....

* Alzehimer's disease :-

(4:30)

it's a Neurodegenerative disease charactarized by Dementia,

that has 3 charectarestics :-

↳ formation of β-Amyloid plaques in CNS

↳ formation of Neurofibrellary tangles inside of it τ-proteins.

↳ Neurodegeneration of cholenergic Neurons in CNS

↳ overstimulation of NMDA Rec. that glutamate works on it, causing exitotoxicity

لو استعملت NMDA بس، ومعه Ach، بتصير حالة مرضية أخرى هي الموضوع.

• Drugs for Alzehimer's Disease :-

↳ Acetylcholinesterase inhibitors

↳ Donepezil

↳ galantamine

↳ Rivastigmine

only these, cause they have higher affinity & Achse in CNS,
the Rest work periphry → though some can penetrate CNS, such as physostigmin that works in Bladder, intestin.

I'm just delaying the progression of the disease,
it will develop!

galantamine can also work on Nicotenic Rec on CNS
not only Muscarenic
so effecting the Autonomic ganglia
so may have higher Adverse effect Profile

Rivastigmine is approved to treat dementia accompanied in Alzeimer.
the only one given transdermal not by oral

Side effects you know

NMDA Rec. Antagonists :-

Memantine

The problem is that glutamate is excitatory Neurotransmitter,
exists in CNS but works in other Rec.s
If it increases it will work on these Rec.'s + NMDA. ⇒ excitotoxicity
↳ Rec. if excited
was Role in Neuro degenerative, Excitotoxicity, Apoptosis

Causes excess Ca^{+2} influx inside the cell
So . ↑ Free Radics
. Degeneration
. Damage of ~~Rec~~ Neurones.

So Memantine that is prescribed to Moderate - Severe Alzeimer's.
Blocks NMDR, prevents Ca^{+2} influx
Meta-Telerabes ⇒ "Doesn't have side effects"

cause the side effects similar to Alzheimers disease.

Used in Combination with Achase

*Pharmacology I :-

* chapter (9) : Anxiolytic and Hypnotic Drugs
- lec (15)

Anxiolytic ⇒ Drugs for Anxiety

Hypnotic ⇒ induce sleep Sedation ... ⇒

Relieving of Anxiety
↓
Sedative effect
↓
hepnotic effect

these are not used for everyday anxiety even if it was chronic.
only used when Anxiety is an unpleasant feeling mixed w excessive fear and apprehension all the time,
"chronic, all the time"

In some cases it's not just mental symptom, but also accompanies w physical symptoms

Sympathetic Activation
Mimetic Action
↑ Adrenaline, Epinephrin

↳ ↑ Heart pumping
↳ heavy sweating
↳ hardening Breath
↳ ...

Drugs used for chronic debilitating Anxiety, when it effects life quality.

1. Benzodiazepines — 1st group
2. Barbiturates

These families are used mainly to treat Anxiety, unlike the neuroleptics that have major use, but also used to treat Anxiety for a side effect they have.

Barbiturates are older and abit worse when it comes to physical, Psychological dependens,
the more a drug have Propability of dependence, the worse it is. "it's Dangerous" ⇒ Tolerance, then addiction.
So they are used for very short period of time if the case needs it

Now this group isn't used that often because there are alternatives, such as Benzodiazepens ⇒ more than one agents
- Some for anxiety
- Some for insomnia
- Other things

3 Antidepressents
Some of Antidepressents are used as the first defense line against Anxiety.

4 other hypnotic Agents :-
Mete New group, Su less problems
Better to be used.

overview of all the chapter

4 Benzodiazepines :- أكثر حاجة اليوم بتتكتب
Used As Anxiolytic, and as hypnotic
"less".
main role is Relief of Anxiety, insomnia
أكثر حاجة تخلك تنام وتكمل النوم

* ضروري :-
Selective ← دواء بيربط موضوعي القلق والقدرة على النوم (مهدئ)
Hypnotic ← دواء منوم وبيخفف على النوم (منوم)

give Anxyolytic, Selective effect,
but Not always hypnotic effect
Sleep cycle تجاوز كمل النوم

- This group is safer, more effective than other groups and there uses as anxiolytic are

if I need a drug to give the calming sedative effect I can use other drugs such as morphines, this drugs are analgesic but can also cause sedation.

I use Benzodiazepines cause it's more save (Fig 9,2)

Safety → 1 → 6

it shows the Ratio B/W the lethal Does, and the therapeutically used does.
the more the Ratio the Better it's a safer drug.
So it's preferred to be used,
though in Some Anxiety cases or

→ 1 ⟹ other groups are used.

*Mechanism of Action :-

Fig (9,3)

Benzodiazepines work on GABA Rec.

it's a ligand gated ion channel CNC
inhibitory → Rec.
linked w Cl^- channel
as we studied.
*you should know that there are Two Types of GABA Rec.
- GABA A ⇒ ionotropic
- GABA B ⇒ Metabotropic "G-protein coupled"
  Muscarone Rs

it Binds w GABA which is inhibitory Neurotransmitter, Cl^- channel is opened So much cloride inside of the cell So Hyperpolarization ⇒ Neurotransmission is the CNS So the Desired inhibition

"Anxiety and insomnia is a type of CNS excitation" Stimulation of CNS

the more inhibition, the better Results w ~~inhibiting~~ Relieving Anxiety.

"that's physiologically Normal, "the Role of GABA at the GABA Rec.

the Role of Benzodiazepam, they are allosteric agonists.

اللي بيرتبطوا فيه ارتباط جانبي بتزيد الـ affinity الـ Rec. الـ affinity الـ GABA الـ Rec. "لجهة" مستقبل الـ GABA بشكل أكبر.

Advantage ~~الـ~~ لتخفيض ← Not Rec

from the fig ⇒ there are 5 Subunits of protein "Rec-GABA"
↳ 2 α → (1→6)
↳ 2 β
↳ 1 γ

بكونوا لاصقين على بعض بشكل بسمح الـ Rec انه يكون لتصف كل بشكل القناة ويتركه عشان اخراج الـ GABA

المرة بيجي الامتحان

Subtypes that Rec can be in different combinations (1,2), (3,4), (1,3)...

The Binding Site of GABA is ⇒ α, β

The Binding Site of Benzodiazepin ⇒ α, γ

Knowing subtypes is important;
you should know that it is an Allosteric
Agonist to Binding Site called
Benzodiazepen Rec. ⇒ "BZ-Rec"

- BZ-1 ⇒ includes α-1 subunits
- BZ-2 ⇒ includes α-2 subunits

> are the Rec.s Benzodiazep
which Bind to, depending
weather the subtype is
1 or 2

after Binding to either, ⇒ ↑GABA
Binding ⇒ so all the mechanisms
that GABA Does.

- ↓ Membrane excitation
- hyperpolarization
- CNS inhibition

(Zolpidem)

it doesn't have any effect on the
duration of Cl⁻ channel open

but it just make GABA bind and does its functions

Barbiturates هذا القوم بيجي وبعدها

*Actions :- (8) عددها ثمانية

↳ Reduction of anxiety
- the most important subunits α1, α2 when the GABA A Rec contains α-2 ⟹ ↓Anxiety, Muscle Relaxant while α-1 ⟹ hypnosis and other things

↳ Sedative hypnotic effect
GABA activity increased in a Rec containing α-1

↳ Anterograde amnesia
فقدان ذاكرة مؤقت للفترة القادمة "متذكر بعدها"
very temporary loss of " confusion memory
also mediated by α-1 | نفس شغل مرخي العضلات لكن مختلف كالتو بيشتغلها peripheral

↳ Anti-convulsant, Muscle Relaxant
• α-1 "seizures" • α-2 Diazepam ↓spasms of "skeletal muscle"

Scanned with CamScanner

the first 3 Actions can be achieved w the normal therapeutic does used for anxiety. "less than the used of sedative hepnotic edites

the last 2 Actions can be Achieved w higher doses.

* Therapeutic uses :- (7)

1. Anxiety Disorders
   - most famous CAD ⇒ generalized Anxiety disorder.
   "highest levels of Anxiety" Requires Benzodizepines
   - Anxiety in genes
   - panic disorder.
   - page 99 → take note
   - Anxiety Related to other things like Depression, Schizophrenia, OCD ⇒ obsessive compulsive Disorder

* for you :-

كلام مش مطلوب

We know that the problem in depression is that there is inhibition to the CNS, how using CNS inhibitors can be useful ?!

The inhibition in depression is in different complicated mechanism "different pathways or different receptors" & gives summation of action, & sometimes need stimulation to prevent depression, at the same time inhibition to prevent anxiety.

A person might be anxious, depressed → in the next chapter ⇒ we will study mania disorder ⇒ Bipolar ⇒ half depression, half over activity.

- there is addiction potential of using this family if used for long period of time

لازم الانقطاع تدريجي لا يحدث Tolerance

very long acting and preferred to use.

- Clonazepam
- lorazepam
- diazepam

] Can take one tablet a day "effective" if ↓ Anxiety & may reduce the Dose and if needed & use it again

بيمنع من الاصابه Seizures بنسبه

* if the drug is long acting, the (tolerance) is lesser.

↳ اما البدء تقع لا تكون عندي اذا كنت قطعت نفس العقل

· Alprazolam "XANAX®", "XANAGIS®"
· used in GAD, All other Anxiety disorders,
But it's the drug of choice in panic attack
· used for ~~long~~ ~~~~ short, long term treatment

عكس الـ short acting يعني تأثيره يطول فيه ٥ كون الدواء لا يكون في الجسم
- less tolerence than others
- intermediate to short acting?

↳ Sleeping disorders :-
these are used for insomnia when the goal is to use drugs that can work rapidly.
يساعد المريض أن ينام
بسرعة أكثر من الـ sedative effect
لأن المريض يحتاج أن يكون sleep induction

↳ temazepam ⇒ intermediate

↳ triazolam ⇒ short acting
(so worse withdrawal symptoms)

*I may prefer Benzodiazepine's member depending on therapeutic use, pharmacokinetics

ex for sleeping:
Short onset ⇒ Triazolam for people who can't sleep.
⇒ Temazepam for people who sleep but نومه متقطع

Difficulty staying sleep => induction Term

Difficulty going to sleep => maintain Term

↳ Estazelam intermediate

↳ Quazepam

↳ Flurazepam > very long acting

↳ for sleeping, used less

↳ Amnesia :-

it's temporary loss of memory when first taken, though it's considered as therapeutic use but ~~side~~ adverse effect, there is drug that causes that more than the drugs.

↳ Midazolam

used cause it causes some Amnesia so it causes Conscious sedation.

Used Preoperatively to facilitate sedation "تهدئة", and use less doses of Anesthetics.

One of Stages of Anesthesia is Amnesia

- Seizures :-
  تشنجات بسبب حرمنة او صرع الصرع
  - Lorazepam
  - Diazepam
  - Clonazepam
    - Adjuvant effect with the drugs of seizures

> Status epilipticus
> "emergency"
> epilepcy

- Muscle disorders :-
  Diazepam

- Dependence :-

القدرة على احداث ادمان

↳ Physical Dependense

الدواء له القدرة احداث ادمان جسدية لما يسحب من الجسم، يتعب الجسم وتحصل "withdrawal symptoms"

↳ Psychological Dependence

هو الاحساس بان Neurotransmitter as well كذا حاجة

شعور بالسعادة فالشخص يعوزه

High dependence is this group and Discontinuation causes withdrawal symptoms & can't suddenly stop it it will effect

↳ heart

↳ Body

↳ Muscle

* they are controlled substances

very Rapid onset, very Rapid Acting

Fig (9,5) => Triazolam is the worst withdrawal symptoms cause it's potent .cause it's the shortest effect الجسم بيتخلص منه بسرعة

الاخذوه الأعلى له الاقصر لما بالنسبة half life => نصف

Adverse effects :-

Since they are CNS inhebitich drugs
they cause CNS inhebitich

- Drowsiness, confusion دوخة وتشوش
- Ataxia at very high doeses
  to effect on the Brain specifically
  the cerebellum تضيع توازن الحركة
  "Coordenatich of movements"
- Cognetich impeirments
  عدم القدرة على التفاعل مع المحيط
- High Tolarence in Some of them
  such as Triazelam
  لو استخدم الدواء لفترة طويلة يقلل من
  التأثير الخاص به
- Metabolized in liver, should be careful
  when given to someone w liver problems
- Contraindicated for people w glaucoma
  such as angle closure glaucoma cause

it increases IOP

"pilocarpin for emergency"

↳ Synergestic effect ⇒ anything that causes CNS inhebition such as Alcohol.

II Benzodiazepin Antagonist :-

if taken in very high doses that it leads to complete of almost complete CNS inhebition it may lead to Respiratory depression ⇒ "fatal"

Anti-dot CNS' ⇐

↳ Flumazenil

↳ an Antagonist that will

- Bind ⓦ GABA Rec. in the place of Benzodiazepine and Reverse the Action.

↳ Bind of Benzodiazepine

- given as I.V in emergency

- very Rapid onset
- Duration is very short
  - So if overdose → very long acting diazepam give it as injection
  - Contraindications ⇒ unwanted side effect vanish it may cause Nausea, vomiting

III Other Anxiolytic Agents :-

- Antidepressants
  - SSRI's ⇒ Escitalopram "cepralex" (P)
  - SNRI's

Though these are Antidepressants, they are the first line for people w GAD.

Can be used alone or combination w Benzodiazepine, so the ADS - P using Benzodiazepine used

less doses.

unlike Benzodiazepines that give Rapid effect, those drugs cause accumulation effect

الذي يظهر بعد فترة من الاستخدام.

. have much lower potential for Addiction.

- Buspirone
  - other Anxiolytic Agents in different Mechanism.
  - work on Serotonin Rec. ⇒ 5HT1A and less on Dopamin D2
  - only useful for long term effect in Anxiety.
  - N.b useful for Acute Anxiety Attack, if the effect is Desired Now.

slow onset, ↑ Duration

- efficacy is comparable ↓ Benzodiazepin and give effect ↓ Anxiety
- the difference is that it doesn't increase CNS depression if given ⊃ Alcohol
- also it Doesn't cause Muscle Relaxation or Anti-convulsive effect even if we ↑ Dose.
- Adverse effect profile is much better than the ~~Benzodiazepin~~ Benzodiazepin.
- No potential Addiction as Much as Benzodiazepin.
- Though, it's not used as often as Benzodiazepin

History

أكثر Benzo

*Pharmacology I

• lec (16)

*Chapter (10): Antidepressants

Antidepression

Decrease in the level of some Neurotransmeters responsable for happy feeling, Activity feeling, Accomplishments.

Most Neurotransmeters effected are: Serotonin, NE, also there is decrease in the levels of Dopamin,

But Dopamin has bigger functions than Reward system

↳ Coordination of Movements

↳ Cognetion ..

- loose the desire of life,
- Suicidal thoughts,
- Mode changes,

- there are several depressive Disorder

↳ Major depression

↳ Bipolar depression

Major depression:
the sever, general depression,
the most difficult type to deal with

cause some times depression depends on
the conditions of patients
ex: postpartal depression that
is specific after birth
as long as the conditions exits
the progresses gene!

But here it's not the same,
not easy to get rid of it

if I started therapy I can't just
stop.

Bipolar - depression:
very serious, not cause it's depression
but cause it's Bipolar. انفصام ←

the person suffers condition of depression,
sadness ⟹ depression in CNS
but at the same time also suffers
CNS Activation, a condition called

Almania ⇒ over - happyness, Much talking
Agressiveness, Anger.
depression

In this case I should use other drugs
Along side the Antidepressants
such as Mood Stabelizers

The use of Antidepressant isn't Just used
for depression,
Also for psychiatric disorders..
Anxiety for example
SSRIs, SNRIs

*Mechanism of Antidepressants :-
these drugs will cause increase in Serotonin or
NE Directly or indirectly.

*Until Today the Antidepressants are based on a
Theory not an evidence.

"The theory of Biogenic Amines"
all Neurotransmeters that are consists
of Amines (NE, Serotonin),
These Neurotransmeters that influences
the Mental health condition.
cause simply depression Results from it

Neurotransmeters,
And Mania is due deficiency in these Neurotransmeters.

Science doesn't Agree to this, 'Cause
If Sc,
when Drug is Long taken, patient
should feel better.

M.C.A aren't lex? understood, immediately
the levels of Neurotransmeter directly increase
but the effects is seen after 2-3 weeks.

* SSRIs :-
Drugs w a Mechanism of Blocking the
~~Enzyme~~ Transporter of Neurotransmeter
Serotonin selectivally No matter the
Does.
Selectivatty to Serotonin Transporter
is 300-3000 times more than that
of NE. (=0)

Since it's Selective,
Side effects Are less, Save in over-does

ss | SNRIs TCAs |

SSRIs

they all have the same Mechanism.
Block Transporter,
inhibit Reuptake

نفس الشي بس
TCAs بتكون مش
كتير Ser - NE
اعراض جانبية كثيرة ∴

Scanned with CamScanner

No. 1 in Depression followed by SNRIs.

the effect of these Drugs Require 2-3 weeks to start appear.

Can't see Max Effect unless 12 weeks pass.

If patient didn't Response to one of them family, May Response to the

- Citalopram
- Escitalopram
- Fluxetine "Prozac®"
- Fluvoxamine
- Paroxetine
- Sertraline

primary therapeutic indication is depression, Might also be used in GAD, all the Anxiety disorders

- Other therapeutic uses :-
  - Fluoxetine used for bulimia Nervosa
    "النهم العصبي"

Eating due to Mental disorders associated with regret feeling, attempts to vomit after Eating

- Adverse effects:-
  - Headeech
  - Anxiety
  - sweating
  - hypertechnia
  - Sexual dysfunction
  - Anxiety
  - GI-Problems

- Sleep disturbances:-
  The group doesn't work the same way, so using Drug for cases is different.

Calming Antidepresent
- Paroxetine
- Fluvoxamin

} Treat insomnia

Activating Antidepresent
- Fluoxetine
- Sertraline

} Treat excessive somnolence

- SSRIs induce sexual dysfunction
Reaches a stage where it should be replaced w Atipical Anti-depressent

- use in children, Teenagers
Must be used carefully, only few cases & can use SSRIs w children
  - Fluoxetine
  - Sertaline
  - Fluvoxamine

used to treat children obsessive - compulsive disorder. اضطراب القهري #
  - Fluoxetine
  - Escitalopram

used to treat childhood depressions

- overdoses:
May cause arrhythmia Citalopram
causing QT-prolongation
Seizures May be

Serotonin Syndrome
↑ Serotonin level too Much Accompanied
ѡ̄
↳ hyperthermia
↳ Rigidity
↳ Clonic Muscle Twitching * (تكفير)
↳ change in Mental State اضطرابات مستمرة
May lead to Death

occurs due to giving Drug that ↑ Serotonin
ѡ̄ other one that also ↑ Serotonin.
ex: MAO inhibitor + SSRIs
almost Contraindicated " يُفضل عدم أعطاءهم "

• Discontinuation Syndrome :-
Stop taking these drugs is Most dangerous
ѡ̄ Drugs that have short duration of
Action.
Doesn't have Active Metabolite.

after Stop taking them, No effect of
these drugs stays in body.
Should Stop taking them gradually

Scanned with CamScanner

*Flexetine has the lowest discontinuation symptoms, cause it has long half life, has Active Metabolites.

See

*SNRIs :-

- Venlafaxine
- Duloxetine

SNRIs :-
- for people w depression
- to people w depression + Muscle pain
- Selective only bone pain

the prevent Reuptake of Serotonin, NE
used to treat depression.
very similar to SSRI's.

& use them for people who didn't Respond to SSRIs in treating depression

also for people w depression accompanied w Muscle, Bone pain Result from Nerv pain.

has Ability to Manage pain.

Best of luck

لانها ترفع Ser ، NE والالم مربوط بال
Set - NE pathways ∴ السيطرة على مستوى ع بسيطر على
الالم . بالتالي [TCA]

• Venlafaxine :-

Blocks Reuptake of Ser, NE but depending on the dose.

low therapeutic doses ⇒ only Blocks Serotonin

Medium - high dose ⇒ Also Blocks NE

Break down w 2D6 — اكو دواء يأثر على هذا الانزيم يؤثر على المواد .

Nausea, headach, May cause sexual disfunction "not like SSRIs"

higher doses ↑ BP.

• Duloxetine

Same as previous, But all doses Block NE, Ser.

Break down in liver, it inhibits 2D6

Atypical Antidepressants :-

They are Antidepressants, but unlike the "Typical" Antidepressants when it comes to Mechanism compare to SSRIs, SNRI, TCAs, MAO inhibitors etc.

- Bupropion
- Mertazapin

- Bupropion :
Though being Atypical Antidepressants, the Mechanism is similar to previous families,
Difference is ⇒ Dopamin instead of Serotonin.
"Reuptake inhibitor" of NE, Dopamin

Along side of Being used to treat Atypical depression that doesn't Respond to any other drugs than SSRIs, MAO inhibitors, it's also used for

people who want to quit smoking
→ prevent withdrawal symptoms of nicotine"

لـ سـ كـرت

· Mirtazapine | ①
it's α-2 Antagonist ⇒ -ve feed back
New Antagonist.
↑ Release serotonin, NE.

also . . ②
it works as 5-HT₂ Rec. Antagonist
which is serotonin Antagonist. ?!!!
↓
it's thought
that Activating
it induces depression
unlike other serotonin
Rec.

③
has very strong Antihistamin Activity
similar to first generation
so high sedation effect.
مـ لما مرضى الاكتئاب عنده مـ كل بالنوم
NO Anti-Muscarinic side effect as in TCA

Scanned with CamScanner

② No Sexual impairment as SSRIs
② it's used as alternative in case of sexual dysfunction.

* TCAs :-

- Imipramine ⟹ #1 for Antidepressant in this group, though Now other Families are used. Due to the S.E Profile
- Chlorimipramine
- Amitriptyline
- Doxepine

This group works in Two M.O.A

- Inhibit the Reuptake of NE, Serotonin
- Block Rec.
  That Mechanism is thought to be Responsible for the side effects not the therapeutic use.
  Blocks Rec include
  - Adrenergic
  - Serotonin (5-HT$_2$)
  - Cholinergic
  - Histamine

Actions and therapeutic uses:-

↳ TCAs can elevate mode, improve depressions in depressed patients.

↳ 50-70% of Morbid-preoccupations "Suicidal thoughts and all Related thoughts"

The effect starts to appear after 2-3 weeks

very slow withdrawal, should be stopped gradually

used to treat Moderate-Severe depressions, panic disorders, Anxiety

• other uses:-

Imipramine | depression, panic disorder, Nocturnal enuresis

used to treat enuresis "Bed-wetting" but only used in children after 6 years.

as an alternative of Amitriptyline

Dizpropramine → Anxiety & Antiemetic Hormone

Amitriptyline
Migraine headache, Neuropathic pain

Doxepin
very good in the ↑↑↑ of insomnia
along side ↓ ↑1, ↑2 uses

- Adverse effects profile:-

↳ Weight gain
Special for TCAs, Mertazapine is the Atipical Antidepressants. Cause they are Appetite Stimulants

↳ Dry mouth, Constipation, Urinary Retention, Blurred vision
Cholenergic Antagonists

↳ Tachycardia, ↓ the static hypertension
Adrenergic Antagonists
Mostly ↓ Imipramin, Directly

↳ Arrhythmic
in high doses, Result from ~~Adrenergic Antagonist~~ TCAs effect.

- Nausea, Drowsiness, Sedation
  Antihistamin effect.

- These drugs have, very Narrow therapeutic index.
  only 5 times the therapeutic dose if Temperature is reached.

- Though they are very useful for depressed person.
  They might be dangerous for patient ⇐ bipolar disorder. اكتئاب ذو نوبات القطبين

- They will worse Epilepsy, Arrhythmia, prostatic hyperplasia.

* MAO inhibitors :- (Rides only)
  - phenelzine
  - selegiline
  - Tranylcypromine

they will prevent Breakdown through MAO, but works inside the Neurone after Neurotransmitter is being Reuptaken with Mean MAO, that MAO Breakdown NE in two ways

↳ NE that is about to enter the visicle

↳ the NE that is out side, will be uptaken

So MAO inhibitors will prevent degradation of leaked Neurotransmitters.

only works in cytoplasm not visicle "MAO"

These drugs have got effect, but they are non-selective,

- so Blocking All MAOs
- prevent Degradation of NE in periphery.
- all side effects of ↑NE
- has dietary Restrictions → DDI FDI (Tyramine الجبنة القديمة)

Are Antidepressants ↩ but not contain

. like others, the effects Needs time
. Selegiline, Tranylcypromine have Amphetamine like stimulant effects.
"Metabolite"

. Can't be used w TCAs, SSRIs
. very useful for Atipical depression that didn't Responds to Anything.

M.O.A:-
Blocking Breakdown of ~~transmitters~~ Neurotransmitters.

Lophenelzine
that is irreversible. body Needs to synthesize New MAO

. Adverse effects
If taken w tyramin that helps in Release of EpiNephrine in the synaptic space.

So ↑↑ Catecholamines in body.
So hypertensive crises

it w other Antidepressants will lead to serotonin syndrome.

If I have to use other Antidepressants should undergo washout period.

* If giving fluoxetin should wait for 6 weeks before giving MAO inhibitor.

Lig 10,10 | take a look

* TTT of Mania, bipolar disorder :-

Since it's part Depression, part Mania

Antidepressants

- Can also use Anti psychotics as Mood stabilizers

Most dangerous SE is on CNS causing slurb speech, Ataxia

↳ bipolar depression

Lithium

Antiepileptic Drugs that have Mood stabilization

↳ Carbamazepine

↳ Valproic Acid

↳ Lamotrigine

Lithium has an unclear
Mechanism
but I think the
it can treat Mania
Acutely, Prophylactically
60-80% effective
Narrow Therapeutic Windo

May decrease thyroid
gland function.
Should be Monitored

* Pharmacology II :- Mostly highlights

بس مفاهيم الي هنا.

· lec (17)

* chapter (11) : Antipsychotic Drugs

↳ Drugs used to treat psychosis, common psychotic Disease :

الذهانية ⇐

انفصام الشخصية Schizophrenia

· Antipsycotics ⇒ also called Neuroleptics or Major tranquillizers

مهدئ كبير ← ↵

مانعة تعطيل Nerv-impuls ↵

· used Mostly in Schizophrenia, also used for Mania, Bipolar.

· these drugs aren't save, they are full of Side-effects,
but using them in Schizophrenic patient is a benifit - Risk Ratio

I chose to inhance the symptoms despite the problems Drug can Make.

Cause they are Nothing compared w what the patient suffers.

*Schizophrenia :-

it's translated to Arabic as "انفصام الشخصية"
though it's not Multiple personality,
other disorder related to psychosis called Multiple personality disorder, that's the one where Multiple personality is

last Manifestation of Schizophrenia is the appearance of other personality

in the early stages the patient will suffer hallucinations, delusions
↳ Auditory hallucinations Mostly
↳ visual hallucinations then

these hallucinations May lead to Suicidal thoughts,
after development in Mental status it leads to bigger problems like the appearance of New personality

· Antipsychotics don't act as cure, they don't cure Schizophrenia 100%, but they control it, Reduce the intensity of hallucinations to less level than without drugs.

· Starts Mostly in teen age to Adulthood "very Rare in children"

· No idea how it happens, it's thought that it's abnormality in Dopamin pathway. ⇒ ↓ Dopamin but not in a level that leads to parkinson's but why? We don't know
Maybe genetic component

* Antipsychotic Drugs :- بسمو الاسم معلمه بالاوهم
↳ first generation
① ↳ low potancy
② ↳ High potancy

(potancy usually describe strength of drug but here it's used to describe affinity

↳ Second generation
⑤

high potancy المعنى لها ... D-2 Rec
as D-2 Antagonist,
higher ...
No it's Related to side effects

ength of drugs but
ere it's used to describe
affinity

High potency المعنى انه المنتج له
له القدرة انه يعطي تأثيرات
لكن المقصود التأثيرات
السلبية
Dopamin Rec لما ارتبط بالـ
low potency drugs الكلام
Dopamin مش هتظهر اعراض
D-2 Rec بنذكرهم
as D-2 Antagonist,

The More the affinity
of Drug the More it
will bind to Rec, it's
thought that it will give
higher effect, but here
no it's Related to
side effects.

- for example parkenson disease Result from ↓ Dopamin levels, and I know that ↓ Dopamin and what it causes is the contention of Muscles.

So one of the most important problems in drug Blocking Dopamin Rec. is by giving parkenson like symptoms as extrapyramidal side effects

↳ high potency

↳ low potency

* First generation Antipsychotic s/ -
also called Conventional, Typical, Traditional. 2nd gen. atypical

the Antipsychotic effect is seen in this generation due to Direct Block of the D-2 Rec 2nd gen. also Block Serotonin

the More the affinity of the Drug, the More potent it's, the More it will be able to cause problems → Haloperidol

high potency

- a low potency 1st generation that effect EPS "Extra pyramidal side effects" is much less is chlorpromazine (low potency)
- When it comes to the first generation in general the efficacy isn't effected weither it's high or low potency the difference is how much EPS it causes.

* Second generation Antipsychotics:-

they cause much less EPS cause they block Dopamine Rec. in weaker manner. ⇒ to a level that is not enough to cause EPS

the bigger effect comes from blocking Serotonin. Rec. Related to psychosis

though they cause other problems called "Metabolic disturbances".

long term use may lead to ① diabetes "Drug induced diabetes"

or lead to ② hypercholesterolemia ↑LDL in blood ⇒ weight gain. ⇒ Mirtazapine + TCAs

*Based on what will I choose the drug?
Since there are 5 drugs in this group?

↳ the 5 drugs have the same efficacy

↳ When it comes to choose from Lista, second generation,
I usually prefer using the 2nd, cause the side effects profile is better.
Doesn't cause EPS as 1st generation does, though it's less potency 1st gen.

↳ also as efficacy 2nd is higher than 1st.

↳ 10-20% of patients won't response to either 1st, 2nd.
I'll use the Drug Clozapine ~~allergy side & other.~~
it's use is limited to refractory patients cause the S.E Profile is really bad.
causing - bone marrow suppression
- seizures

- Cardiovascular side effects
- Agranulocytosis ↓WBC.

* Mechanism of Action:-

- Dopamine Antagonism
  Block D-2 Rec "Mostly 1st gen"
  "less 2nd gen"

- Serotonin Blocking Activity
  Blocking 5HT Rec which is Serotonin Rec, have many subtypes, each subtype A, B, C ..
  here the Block on 5-HT$_{2A}$
  "2nd gen"

* Actions:-

Come from Blocking
- ↳ Serotonin "2nd gen"
- ↳ Dopamine

but it will also cause other things "similar to non-selectivity problems of Anti-depressants" TCA Alfa Adrenergic, Cholenergic, Histamin Rec. "

1- Antipsychotic effect:-

Which is the Main therapeutic use

Comes from the Management of $+ve$ symptoms of schizophrenia, $-ve$ symptoms of schizophrenia.

↳ $+ve$ symptoms
the known, real symptom of schizophrenia which is sever hallucinations.
but not every schizophrenic patients starts with the same severity of hallucinations,
Maybe some patients have some Mental disorders but not exactly schizophrenia disorders but not ...
so it's :

↳ $-ve$ symptoms
having No feelings at all Apathy, Cognitive impairment, ~~Mental~~ Mute swing, Blunted effect

الشخص بطل يحس [illegible] أفكار، حزن
فرح ... الخ

تقلبات مزاجية شديدة جداً دون [illegible]
[illegible]
[illegible].

Disease is Mix of both $-ve$, $+ve$ symptoms both are bad.

• 2nd gen was used to cure -ve symptoms more than the 1st gen

• 1st gen only the +ve symptoms, the hallucinations, their severity → +ve Side effects

* Most drug give Results in -ve symptoms Clozapin that we used in Refractory patients, cause -ve symptoms are caused by Refractory disease

II - Extrapyramidal Effects:-

they are Adverse effects as an Action

EPS: it's a Motion problem in parkinson like symptoms ⊕ Dopamin

Tardive dyskinesia: effects Movement of face, Jaw is Mainly. "involuntary facial Movements"

Chronic irreversible use

Most common in 1st gen than 2nd Atypical D-2 Rec affinity low

III - Antiemetic effects :-

therapeutic use, for Nausia, Vomiting
& can use all the family cause they
block Dopamin Rec in the chemo Rec.
trigger zone (CTZ) where Activity
it is who causes Nausia, Vomiting

Except for Aripiprazole that is a
partial Agonist it can block dopamin
in certain level with showing effects
of showing it.
but can't used in the Antiemetic
effects.

~~IV~~ - Anticholinergic effects :-

only found in
↳ chlorpromazine
↳ Clozapin
↳ Olanzapin

Adverse effects

V- other effects :-

Lig

* therapeutic uses :-

↳ TTT of schizophrenia as Antipsychotic effect

1st ⇒ +ve

2nd ⇒ -ve more

Atypical Antipsychotic 2nd gen the more effective

work on $5HT_{2A}$? effective more for people don't respond to 1st gen

↳ prevention of Nausea, vomiting

mostly prochlorperazine

↳ other uses :-

chlorpromazine very effective in curing intractable hiccups

المازوقة الغير معالجة الي بتأثر عل الحياة

& can also use Anti-psychotics as mood-stabilizer

for people with Bipolar disorder, mania

* Adverse Effects :-

بس الأعراض دائم تكون

↳ EPS

Block dopamine

parkinson like symptoms

↳ Tardive diskinesia :-
irreversible, require stop drug
involuntary facial movements, jaw

↳ Neuroleptic Malignant syndrome
fatal rare appear in some few people
using Antipsychotic.
& should stop drugs

↳ change mental status
↳ fever
↳ Muscle rigidity] لأن الأدوية Neuroleptic

Succinylcholine less Malignant hyperthermia نفس

. نفس الـ

Fig 11.8

أنتشر
بالفعل

Rec 100 غلط

*Pharmacology I:-

- lec (18) + (10 slides)

*chapter (12): Drugs for Epilepsy

Epilepsy:

It is Most common Neurological Disorder,
Causes are unknown.
So it's harder to treat.

it's accompanied w overactivation, desynchronizing in the CNS level,
Due to (Video firing) in Neurone
"paroxesmal" - Successive. the whole time there is Active Action potential
No Rest!

the problem isn't the Release of Neurotransmitter but what follows that:
↳ Na^+ voltage channels open
↳ Ca^{+2} " "

& A.P that keep Repeating
"Successive Activation."

So as Result:-

Seizure

that has different forms, Doesn't always mean contraction of muscle
* the common form of it is muscle contraction.

the form depends on the type of Seizure,
different ranges of signs, symptoms
patient may

↳ lose consciousness
↳ involuntary muscle movements
↳ convulsion تشنج/نوبة
↳ hallucinations
  ↳ visual
  ↳ auditory
  ↳ olfactory

بشم روائح معينة مرتبطة ب حدوث النوبة

Epilepsy

↳ Result of unknown cause
Idiopathic

↳ Cause that I can't Treat
following Major Accepters,
Trigger ..

if I know cause, I treated that
cause.
No Need for Antiepilepsy Drugs
But these cases ∵ unknown cause
it's chronic,
Must use these Drugs all the time

~ 75% of cases Respond to the
Drug therapy.
- Monotherapy is enough

*Etiology of Seizures, Classification:-

Seizure:
Very strong Activity of Neurons in the Brain.
"Paroxysmal Firing"

هذا الوصف العام بشكل عام
لكن ما يسبب النوبة الصرعية
يعتمد نوعها.

it Might be in a part of the Brain, or Maybe the whole Brain

the generalized Many Starts as focal "بؤرية" the area of that focal determines the Type of the seizure.

حسب أين البؤرة
التي تبدأ منها
الأعراض متنوعة.

ex: if the Motor cortex is the area effected:
Convulsions, Combustions
"Combustive seizure is not the" Major Seizure

*depending on the phenomena in the partial,
determining type of seizure

if seizure is generalized, 90% of cases it's compulsive "Motor cortex must be effected"
abnormal involuntary movements with contractions in muscles, relaxation in certain moments

if partial, it depends.
↳ for example: effected the auditory lobe, Olfactory lobe...
even it might be psychological

IPSP + EPSP → Balance! - summation for Action

here → EPSP wins, too much excitation

So as therapy in general
↳ ↑ inhibition
↳ ↓ Excitation

Scanned with CamScanner

Classification of Epileptic Seizures:

- Local "Partial"
  Means part of Brain is effected "Local point"

  - Simple if the area effected certain Neurons, ex Neurons of Motor Cortex only
  - Complex, other areas but Not the whole Brain so still Local

- Generalized
  includes the whole Brain, But the symptoms of Seizure May Seen is 6 Cases

  - Tonic-Clonic
    generalized seizure
    Tonic part: continuous contraction
    Clonic part: Very Sever contraction in a second then Relax

- Tonic
  تشنجي
- Clonic
  تشنجي

*Usually these seizures 2-3 Minutes then loss of consciousness

- Myoclonic :-
  Short episodes of اختلاجات Tonic
  & Contraction
- Atonic :-
  Suddenly the Muscles relax Letharg by drop of the patient "Drop Attacks"
  يوقع نفسه بحيث يمكن يغمى عليه

اول 5 انواع بنفهم نفس النوع

- Absence
  Blanking out "eyes opened but he is not there"
  No blinking
  *Limited in Age

نوبات الاطفال

* MOA of Antiepileptic Medications:

- ↑ inhibition
- ↓ excitation

↳ Block voltage gated (Na^+, Ca^{++})

↳ Potentiate GABA

↳ Activation of GABA

↳ interfering the glutamate Rec. that

Reacts to excitatory → NMDA Rec.

↳ Two drugs

↳ Multiple targets on CNS

SV2A Block

* These Drugs don't cure Epilepsy, but suppress it.

* Drugs Selection:

There are old, New generation, Broad drugs are all used.

Use depends on the type of seizure, age & patients, other diseases, physiological "pregnancy".

* usually I prefer using Mono therapy Medication.
  - ⇧ Adherence
  - ⇩ Side Effects.

* Antiepileptic drugs in least DDI
  - Levetiracetam ⇒ SVAZ
  - Gabapentin
  - Pregabalin

  > Analgesia (opioids)

for example useful for elderlies using polypharmacy

* Don't start therapy in the first seizure,
if repeated only ✓
⇒ first choice drug ✓
↳ if 3rd seizure occur
↳ if other seizure ?
⇒ I use other monotherapy, بس أقدر
or I use other drug
along side with it
"gradually بوقف A لحد ما صار دوا B وينقص الوقت بيبدأ الدوا D لحد ما يوصل ل therapeutic dose of B"
I don't leave the patient wherever.
⇒ I expect that seizure now free
⇒ if not !!!
I know that switching to other drug isn't enough so I switch to other drug ⇒ combination

if the combination of Tw - 3 drugs
Didn't work,

⇒ Now I Need Vagal Nerve
Stimulation "Surgery"

• Mechanism (Ner to Me) :-
an Area in the Neurones called : synapse
Visicle proteins ZA

SVA2

it's thought that this proteins must be
Activated,
So Neurotransmeters are Released
Ca enough only Ca++ ...

So Drugs Must Block this Proteins

*only the Drug targets this Mechanism

Antiepilepsy Medications :-

The only difference BTW New, old is the Adverse effects Profile, pharmacokinetics but efficacy is the same.

"Might be used More than the New"

~~Drug~~ Most of them Associated w hypersensitivity Rxn

- **Benzodiazepins :-**
  You know the Mechanism!

  - Clonazepam
  - Clobazam

  ] Adjuvants to other drugs

  - Diazepam
  - Lorazepam

  ] used in Status Epilepticus in Emergency, or Prolong Tonic-clonic Emergency (IV)

. Carbamazepine:-   [illegible]

↳ Blocker of Na^+ - gated Voltage channel
So prevent A.P

↳ very effective in focal, generalized Tonic - Clonic

↳ Mentioned in Antipsychotics Antidepressants in Mood stabilizers Controls Manic part of bipolar disease

↳ potent enzyme ~~inhibitor~~ inducer

↳ induces it's own Metabolism "Auto-inducer"
لازم ارفع الجرعة شوية و ما اوقفهاش فجأة

So DDI

* Adverse effects:-
hyponatremia in elderly (prophylaxis)

Contraindicated w Absence Seizures
will worsen it.

• Ethosuximide:-

↳ inhibitor of voltage gated Ca^{+2} channel

↳ effecting in Absence seizure

• Felbamate:-

↳ one of the drugs with broad spectrum of Mechanism of Action

• Felbamate, Topiramate are the only drugs that can effect NMDA.

• Close Na^+ gated voltage channel

ما بسكرش الـ NMDA مباشرة بس هو بشتغل
له Antagonist الـ glycine
الي هو Co-agonist لـ NMDA.

لما بربط الـ glycine الـ glutamate rec بـ
بصير بشتغل الـ glutamate

- Block Voltage gated Ca^{+2} channel
- potentiate GABA Action.
- effect cytochrome enzymes inhibits some induces some
- Since it works with different Mechanisms
  - ↳ Refractory patient
- Adverse effects
  - ↳ Aplastic Anemia
  - ↳ hepatic failure

- Gabapentin:-
  - ↳ ↓ Adverse effects, interactions
  - ↳ but Not Really strong in seizure so used Adjuvant in focal only
  - ↳ other use is useful for Neuropathic pain. "postherpetic Neuralgia" viral infection "حزام ناري"
    هو فايروس بيضرب الاعصاب

Structure similar to GABA, so Direct Agonist on GABA, we expect that. Though, it doesn't !!!

Mechanism is unknown

Used for Petit mal SE

- lamotrigine
- Most famous drug used
- effective, doesn't have NDT
- less Adverse effect
- Blocks Na^+, Ca^{+2} channels
- First line, cause it treats
  - to Focal
  - to generalised
  - to Absence

*Used as Mood stabilizer in Bipolar, Mania

ther given w

↳ Carbamazepine

↳ phenobarbital

enzyme inducer, affect enzymes Break it down

though if given w Valproic Acid the lamotrigine levels

in both cases dose adjustment gradually

~~البوفو سنوات السلام~~

الباقي في السلايدات

:

.

Successive activation

*pharmacology I :-

• lec(20) final lecture :)

*Chapter(14) = opioids :-

↳ the opium plant "الأفيون",
we extract the A.I
"Morphine" that is the one
that represents the opioids

opioids are "Narcotics"
the goal of using them
is Anesthesia "Analgesics"
- Management of pain -

pain diagnosis is only based
on asking patient how
he feels only.
Nothing can measure the
amount of pain,

based that we can can divide
the cas to

↳ Nociceptive pain (NSAIDs)
↳ Neuropathic pain (Ant
↳ Malegnant | non-malegnant pain

الم ناتج عن تحفيز ال periphe Nociceptors

ناتج عن Damage في الاعصاب ، شعور الحرارة والحرقة

وصل الى مرحلة شديدة من الالم يشابه الم مريض ال Cancer .

pain|

unplesent sensation, due to complex Neurochemical procces started in the CNS, PNS togather.

لو في stimulus وانا بجرح الجلد PNS بيوصل اشارة
لل CNS واللي بيرجع باشارات تخليني احس بالالم
الى حد ما.

↳ Nociceptive ⇒ NSAIDs "Declopher, Profen"

↳ Neuropathic ⇒ Anti-Epileptic "gapapentin, pregabalin"

SNRIs ~~"geleesepin"~~

if too much pain → (opioids)

↳ Narcotics, work on Rec in CNS.

they're called Morphin-like, cause it's the first one that was discovered

↳ very strong Analgesia

↳ Euphoria feel

. physical - psycological depend,

. Tolerance ↑ dose in time الادمان ↳ سبب الادمان

. pain when stop it

↳ Withdrawal syndromes
even worse than barbiturates
but..
it's Time limited

لو صبرت ايام بطلع سهل الادمان
الانسان بس اما الادمان
موجود.

opioids can bind to opioid Rec., these Rec. were called that according to the endogenous opioids.

↳ for binding to these Rec, so Managing the pain.

↳ Dynorphins
↳ Endorphins
↳ Enkephalins

] if not there even a small pain will feel like huge one
substance b, glutamate صو افراز

Morphine-like drugs all work the way they do.

the Most dangerous thing when using this family is the hazard of Addiction,
so we will discuss Antidotes & Antagonists used in case of Addiction.

overdoses leads To Death due to Respiratory depression, by Closing the Respiratory center in CNS, so No sensation of CO_2, O_2 levels.

Remember this!

*Mechanism of pain:-

To feel pain there is stimulus works on the Nociceptors, Nociceptive starts at the periphire, No pain in CNS "yet".

So for pain sensation to start, the signal should start in Spinal cord then to thalamus, hypothalamus in Brain.

Nociceptive that started with certain stimulus moves through sets of Neurones, causing firing to Action potential Reaching ⇒ "first order Neurones" that will be the completers of Neurones in periphery

Reaching dorsal-horn of spinal cord that is full of Neurones.
giving sight to the thalamus, so. (pain sight)

learning excitation, Neurotransmeter Release, Leading to Action potential.

Since it's excitation, the Neurotransmeters involved are: glutamate

Fig 14,4: excitation of Pain

In the Neurone, there are excitatory Neurotransmeters, Neuromodulators.

in this case the Neurotransmeter responsible for pain sensation is glutamate, and the Neuromodulator that will help it, give the same effect but a different rec. is: Substance P.

the pain sensation starts when entering the dorsal-horn area,
very strong Activation,
Much Neurones, these Neurones include vesicle, inside it: glutamate Substance P

Action potential ⇒ Na^+ Voltage gated channels openers. So Na^+ Reaching threshold, so Na^+ Ca^{+2} channels opening

…tery of Ca^{+2}, vesicles surface is Now the Releasing glutamate, substance P

glutamate binds with it's Two Rec.

- ↳ AMPA → when stimulate open Na^{+} → & propagation of New AP to the Next Neurones. "Series of Neurones" sending AP to each other
- ↳ NMDA → when stimulated open Ca^{++} channels

Exito-toxic effect of Activated Too Much. pain ⇒ Malfaction & Toxicity

- Substance P (excito-toxicity of pain), binds with Rec. called Neurokinin-1. that will do the same thing open Na^{+}, Ca^{++} channels but indirectly through protein kinases. "enzymes"

- So as Result of all that ↑ excitation which is the pain.

Scanned with CamScanner

the opicits will cancle that by binding
w Receptors ⟹ Gi-protein coupled Rec.

also by effecting ion channels.
So as if opicits has 3 mechanisms

Eeach Neurone includes opicit Rec.
- M mu
- K kappa
- δ delta

↑ order of pain Relife

these three Rec. offer Analgesic effect
when excited,
when opicits stimulate them

different spreading along CNS ⟹ Brain, spinal cord

M-Rec ⟹ is Gi-protein coupled.

in case of the Much Release of glutamate substance P
there will be pain sensation.
M-Rec presents both presynaptically, postsynaptically
when there is Binding w M-Rec there will be
① Blocking of Adenylyl cyclase

(M)

(2)

- Postsynaptically, opioids open K^+ channels "It's thought to be a complement effect" the Actual Mechanism still uncertain. So K^+ outflux so losing the +ve charge inside.

Hyperpolarization ⟹ So the excitation decreases

(3) Presynaptically Blocking the Ca^{+2} - channel, so prevent Ca^{+2} influx so prevent Release of glutamate, Substance P

- all opioids including those inside the body will work the same way

Fig III, 2 :- ✓

- Natural
- Semisynthetic
- Synthetic

(11)

* Actions of opioids :-

- Analgesia ⇐ want to Relief pain without Reducing a level of Anesthetics

one of Anestatics levels is Analgesia "
opioids offer pain relief without loss consciousness, unless ↑level ⇒ بعمل تنويم

انا خو البرية العلاجية ، لا اتوقع انه يعمل كتنويم
بسبب الواهم
~~تحكر انو انا لا اوجع~~

تذكر ، انا لا اشعر بالالم الا لو threshold
الالم انا وصلته ، دور opioids الي بتعمله انها بترفع مستوى threshold.

بصير محتاج A.P strong Nociception اعلى واقوى عشان اشعر بالألم.

اي ان الالم موجود لكن pain perception انخفض
اي يكون في pain بس اخف بكثير.
هنا بنحكي عن Malegnant حتى العلاج.

Depression of Cough Reflex
Not All opioid can work as Antitussive
it's basically Morphine Action.
but mostly they use Codeine in cough syrups.
it has Analgesic effect but weak Analgesic effect compare to other members of family.
Should be used in high doses ⇒ Dependence!

- Miosis
  Constrictive of pupil, which is a characteristic of opioids.
  The pupil is pin point, characteristic of Morphin Abusers. "Toxicity sign"
  Cause Miosis is direct stimulation of M, N Rec.

- Euphoria
  feeling very happy, GABA suppression, ↑ Dopamin levels.
  Causing psychological dependance

- Does dependent Respiratory depression w overdoses, theoretically ∄ Need ↑ does in case of Tolerance.
  ↓ Incident of Respiratory depression

  centrally Acting مركزي الفعل
  تثبط المركز التنفسي بـ CO_2 / O_2

- Emesis, Nausia :-
  by stimulating the chemoRec. trigger zone "Area in Brain" to stimulate Vomiting

CTZ

GI Tract:-

↓ Gastric Motility, gut, Bd

If I Need them as Antidiarrheal effect that's Therapeutic use.

if Someone suffers Constipation, it's an Adverse effect.

Loperamide ← opiates ال زي ادوية تو
opioid-like ттт of Conc.
شغلها الـ CNC مش هتوصل علشان مش opiat

→ Mostly caused by Codein so given laxative c̄ Codein.

CVS

all of opiates except of pethidin cause Bradycardia c̄ hypotension → علاج

Meperidine

مع ↓ ← مقعود/cold

Tachycardia يعمل

Histamine Release in Morphine, Meperidine in higher doses

Pethidin

Scanned with CamScanner

→ Bronchoconstriction, Vasodilatation ← Allergic

Asthma

Tolerance | physical - psychological dependence

Respiratory depression

Therapeutic effect, Adverse effect

Euphoria

5 أيام

* Fentanyl | Alfentanil

synthetic Morphine / synthetic Pentazocine.

Completely synthetic but gives 100 Times More Analgesia than Morphine.

Pre | Post operatively

by Inject

• it's lypophylic, so gives its effect in very short time, this gives the effect of Analgesia, Anestesia

هاي بحطها التحرير بسبب تركيبه

(١٪) طبعاً لازم اعطيه صغير جدا حكو بحطه

• IV, Epidurally, intrathecally (spinal cord / داخل النخاع) — Directly in the CSF

↳ Epidural
أو الـ space المحيط
فيه ضمن ... في خلال
serous spinal fluid

the goal is is offer high Analgesia fast entery to CSF.
used Mostly in Birth pain so local Anestagia.

لو I.V بخدر الجسم كله.

* Methadone :-
opioid works on M, with Additional effects to Block NMDA. "Just for pain exited by glutamate"

Additional Mechanism SNRI, serotonin - NE have Role in pain sensation

So SNRIs work on pain.
Same here opioid works on M, Block NMDA also give SNRIs effects
So very high Analgesia.
that's why? It doesn't only work on Malignant pain, but also the Neuropathic.

* Pethidine: "Meperidine"
for Acute pain works on kapa, so Analgesia, but KAPA Activation is Accompanied with side effects.
"Tachycardia" ممكن نفسر تفسير الدوخة لانو عنده
الـ affinity لـ kapa أعلى من M

has Anticholinergic side effects
↳ Blurred vision
↳ Urinary Retention
↳ Delirium هذيان
Mydriasis?!

Scanned with CamScanner

Adverse effects of All opioids :-

- Hypotension
- Anxiety | Dysphoria

Metabolism [illegible] Euphoria
[illegible] dysphoria

اول ما يشغل ال Tolerance ال
للمواد بيصير شعور ال
بدونه المواد.

- Urinary Retention
- Constipation

} Anticholinergic

- Nausea
- potential for Addiction
- Sedation
- Respiratory Depression ↑Doses

* other Analgesics :-

centrally Acting, but binding power, is 1/6 as strong as the Rest of family.

- Tapentadol

μ Agonist, but not as strong as Morphine

also prevents the uptake of NE
- used for Moderate - Severe pain
- Acute, Chronic
↳ cancer, Neuropathic
↳ post operatively

- Tramadol :-
- Same exactly as previous
- SNRI
- The thing here is that it will give effect, after being Metabolized in the liver Metabolites will be produced that are stronger than the parent compound "stronger affinity on M than Tramadol"

لازم اكون فاكر انو كل تشغيل للـ M ضعيف

"Not pro-drug" give ↑ efficacy and ↑ Duration of Action.

- gives effect in lower level than opioids, so I keep the stronger agents of the case needs that and Respiratory depression very

weak,
. Similar in all other things.

* Antagonists:-
Reverse the effects of Morphine like Drugs in cases of over-doses Respiratory depression.

↳ Naloxone ⟹ used more though The duration of Action is less
↳ Naltrexone

. works as Antagonists on the (3 Rec) M, K, δ. compete with opioids take there place

. higher affinity than opioids

. highest affinity to M which is Mainly involved in Analgesia, Respiratory depression

اسم التراكيدول لا تنكرها اخر كلام نشتغل عليه SAFE { ا.د. نفرض ل Anti-dote تبرج التنفس طبيعي ويرجع الالم لكن هل يلي انو انقذ.

كل مرض السرطان
مش مشكلة لأنه الجرعة
لازم تكون ادقه
لأنه حالات ميؤوس
منه.
بنافع باشي اصلا لانه
كل همنا انو نسكن
الالم

having very short duration,
if he develops it really might
I should give it infusion
if not the case with Bolus to worse

• Naltrexone :-
I Avoid it since it's hepatotoxic
only uses if there is a reason
not to use the first one