Typical / conventional antipsychotics

- Other Adverse effects
  - Neuroleptic malignant syndrome (NMS)
    - Rare but serious reaction, 0.2% of patients on neuroleptics
    - High fever, autonomic instability, mental status changes, leaden rigidity, elevated CK, WBC, myoglobinuria
- **Risk factors:**
- Age, male sex, Dementia, Dehydration, CVA, lithium

Neuroleptic malignant syndrome

- **Rigidity**
- **Hyperthermia** (homeostatic eg. labile BP, diaphoria, tachy, incontinence)
- **Confusion** (altered consciousness up to coma, dysphagia, mutism)
- Raised CK
- Misc (incontinence, dysphagia)

- **Treat in ICU if severe:**

- Bromocriptine 2.5mg BD + dantrolene 50mg IV

- **Prognosis:**

- 30% will have it again upon rechallenge with antipsychotics
- Use low potency agent, wait 14 days, monitor carefully

Typical / conventional antipsychotics

Other Adverse effects

- Neuroleptic malignant syndrome (NMS)
  - After symptom resolution
    - Some suggest to wait for at least 2 weeks before resuming
    - Use lowest effective dose
    - Avoid high potency agents
    - Consider atypical antipsychotics
      - However, NMS has been reported from patients taking clozapine, risperidone, olanzapine and quetiapine

Antipsychotic side effects

ECG changes

i. Most seen with thioridazine, clozapine and ziprasidone
ii. Drugs have quinidine- like effects – QT prolongation, ST depression, increased HR
iii. Get baseline EKG in patients >50 years of age
iv. Do serum K^+
iv. D/C medication if QTc>500 msec

Dermatological

Increased photosensitivity – especially with chlorpromazine
ii. Pigmentation changes with chlorpromazine
iii. Rash – seen within first eight weeks

IM chlorpromazine abscesses

Common drug interactions

Anti-cholinergic	Delirium Paralytic ileus
Sedative	Respiratory depression
QTc	Torsade de pointes
Seizure threshold lowerers	Seizures
Hypotensive	Hypotension

Typical / conventional antipsychotics

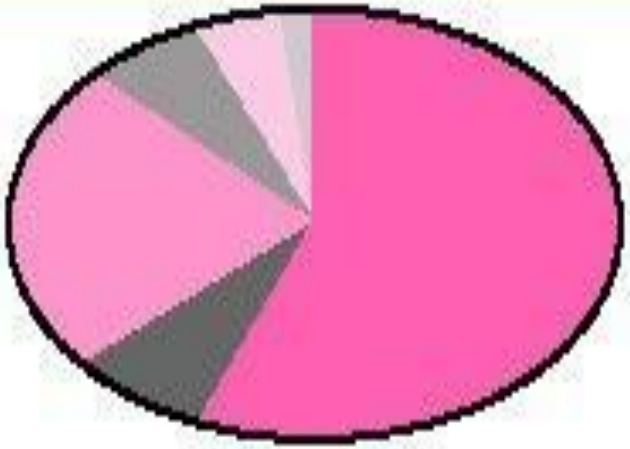
Potency	Drug	Equiv oral dose (mg)	EPS	Sedation	Anticholinergic s/e
Low	Chlorpromazine	100	Moderate	High	Moderate
	Pericyazine	NA	Low	High	Low
	Thioridazine	100	Low	High	High
Moderate	Perphenazine	10	Moderate	Moderate	Low
High	Trifluoperazine	5	High	Low	Low
	Thiotheixene	2	High	Low	Low
	Fluphenazine	2	High	Low	Low
	Haloperidol	2	High	Low	Low
	Pimozide	0.5	High	Moderate	Moderate
	Sulpiride	200	Low	Moderate	Low

Typical / conventional antipsychotics

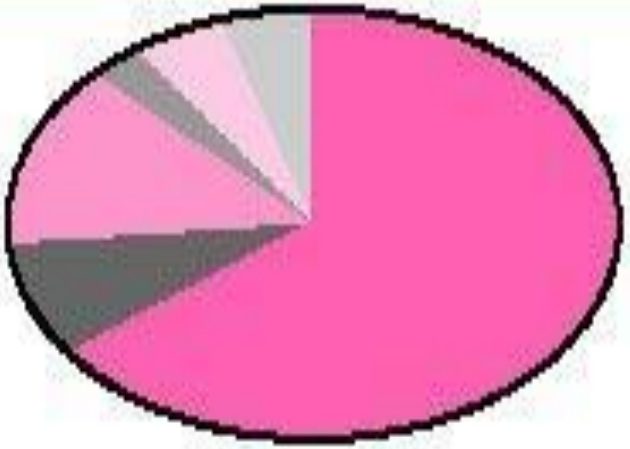
Comparison of representative antipsychotics		
Drug	**Advantages**	**Disadvantages**
Chlorpromazine	Generic, inexpensive	Many adverse effects (esp. autonomic)
Thioridazine	Slight EPS, generic	Cardiotoxicity (QT prolongation)
Fluphenazine	Generic, depot available	(?) increased tardive dyskinesia
Thiothixene	(?) decreased tardive dyskinesia	Uncertain
Haloperidol	Generic, injection and depot A/V, few autonomic s/e	Prominent EPS

Typical / conventional antipsychotics

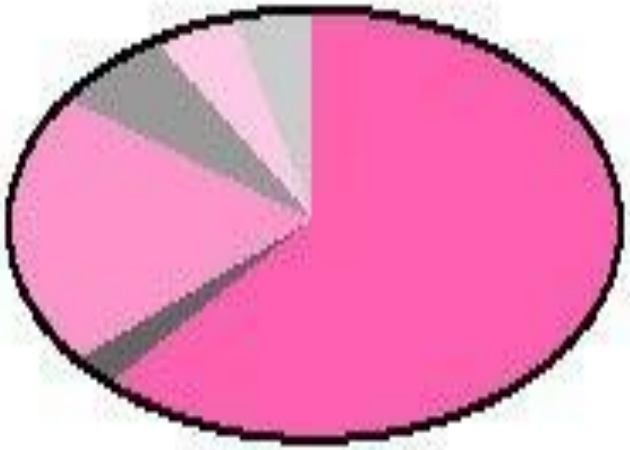
Receptor blockade and Adverse effects	
Receptor type	Consequence of blockade
D2 dopaminergic	Extrapyramidal symptoms; prolactin release
H1 histaminergic	Sedation
Muscarinic cholinergic	Dry mouth, blurred vision, urinary retention, constipation, tachycardia
Alpha1-adrenergic	Orthostatic hypotension; reflex tachycardia
5-HT2 serotonergic	Weight gain



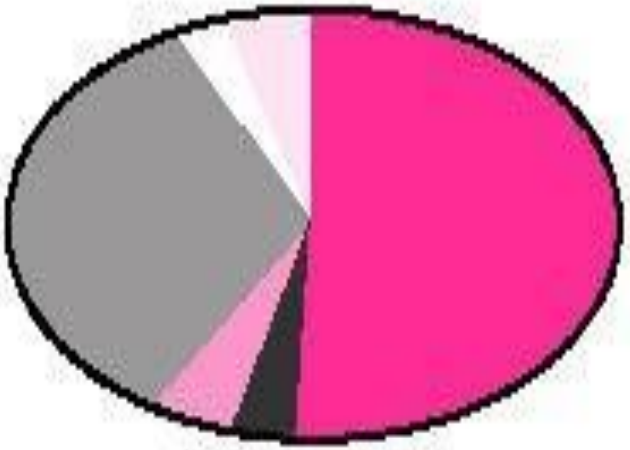
Promazine



Thioridazine



Clotiapine



Haloperidol

- Muscarinic
- α_2
- D_2
- α_1
- 5-HT
- H_1
- $5\text{-}HT_{2A}$
- Sigma site
- D_3
- D_4

Typical / conventional antipsychotics

Other Adverse effects

- Prolactinemia
  - D2 receptor blockade decreases dopamine inhibition of prolactin
  - Results in galactorrhea, amenorrhea, loss of libido
    - **Managed with bromocriptine**
- Sedation
  - Administer once daily at bedtime
- Seizures
  - Haloperidol has a lower risk of seizures
  - Anticonvulsants (beware or possible interaction with antipsychotic)

Tardive dyskinesia

Movements	**ANY movement disorder except tremor!** Choreiform Athetoid Dystonic Stereotyped Affected by emotional arousal **80% of cases are in lower third of mouth** Buccolingual masticatory syndrome: esp. in the elderly Limb/truncal movements more likely in the young Respiratory muscle (belching, grunting, irregular breathing)	
Risks	Duration, dose of antipsychotic D_2 affinity , OLZ, RISP Age esp. women Developmental delay Substance use esp. alcohol Diabetes Smoking In Asians	**DRUGS** Not clozapine Li L-dopa Stimulants Antidepressants Anticonvulsants Anticholinergics*

Antipsychotic side effects

Hepatic

i. Usually asymptomatic elevations in ALT
ii. Not dose related
iii. Usually in patients <50 years old
iv. Can cause cholestatic jaundice – usually in first month

1. Resolves with D/C of drug without damage
2. Most commonly seen with chlorpromazine (0.1-0.5%)

Ophthalmic effects

i. Blurred vision or narrow angle glaucoma secondary to anticholinergic effects (see anticholindergic side effects above)
ii. Corneal and lens changes can occur with phenothiazines, especially chlorpromazine and quetiapine

Differences among Antipsychotic Drugs

- Chlorpromazine: $\alpha_1 = 5\text{-}HT_2 > D_2 > D_1$
- Haloperidol: $D_2 > D_1 = D_4 > \alpha_1 > 5\text{-}HT_2$
- Clozapine: $D_4 = \alpha_1 > 5\text{-}HT_2 > D_2 = D_1$

Receptor Binding Profile of Antipsychotics

	Haldol	Cloz	Risp	Olanz	Quet	Zipras	Aripip
D_2	0.7	126	4	11	770	5	0.45*
5-HT_{2A}	45	16	0.5	4	31	0.4	3.4*
α_1	6	7	0.7	19	8.1	11	47
H_1	440	6	20	7	19	50	61*
M_1	>1,500	1.0	10,000	1.9	1,400	>1,000	>10,000

Data represented as Ki (nM).
*Data with cloned human receptors.
Bymaster et al, 1996; Seeger et al, 1995; Arnt & Skarsfeldt, 1998, Goldstein 2002.

Differences among Antipsychotic Drugs

- All effective antipsychotic drugs block D2 receptors
- Chlorpromazine and thioridazine
  - block α1 adrenoceptors more potently than D2 receptors
  - block serotonin 5-HT2 receptors relatively strongly
  - affinity for D1 receptors is relatively weak
- Haloperidol
  - acts mainly on D2 receptors
  - some effect on 5-HT2 and α1 receptors
  - negligible effects on D1 receptors
- Pimozide and amisulpride†
  - act almost exclusively on D2 receptors

Atypical antipsychotics

Beyond dopamine

- New generation antipsychotics affect serotonin as well
- Glutamate antagonists can help with negative symptoms
- Schizophrenia likely affects a host of systems perhaps by disturbing a fundamental balance among neurotransmitters

Atypical antipsychotics

- Amisulpiride (Solian®)
- Quetiapine (Seroquel®)
- Ziprasidone (Zeldox®)
- Risperidone (Risperdal®), Risperdal Consta
- Olanzapine (Zyprexa®), Zypadhera
- Clozapine (Clozaril®)
- Aripiprazole (Abilify®), Xeplion

Atypical antipsychotics

- Mechanism of action
  - Similar blocking effect on D2 receptors
  - Seem to be a little more selective, targeting the intended pathway to a larger degree than the others
  - Also block or partially block serotonin receptors (particularly 5HT2A, C and 5HT1A receptors)
  - Aripiprazole: dopamine partial agonist (novel mechanism)

    Partial agonist effects at D2 and 5-HT1A receptors

Atypical antipsychotics

Relative receptor-binding of atypical antipsychotics						
Drug	D1	D2	5-HT2	α1	M1	H1
Clozapine	++	++	+++	+++	+++	+
Risperidone	-	+++	+++	+++	-	+
Olanzapine	++	++	+++	++	+++	++
Quetiapine	-	+	++	+++	+	+
Ziprasidone	+/-	++	+++	++	-	+
Aripiprazole	+	+++	++	++	-	+

Mechanism of Action

- **Atypical antipsychotics** (serotonin-dopamine antagonists) are antagonists of D2 and serotonin 2A receptors, but they can affect many other types of receptors.
- Atypical antipsychotics:
  - D2 receptor blockade of postsynaptic in the mesolimbic pathway reduce positive symptoms
  - Enhanced dopamine release and 5-HT2A receptor blockade in the mesocortical pathway reduce negative symptoms
  - other receptor-binding properties may contribute to efficacy in treating cognitive symptoms, aggressive symptoms and depression in schizophrenia

Differences among Antipsychotic Drugs

- Clozapine
  - binds more to D4, 5-HT2, α1, and histamine H1 receptors than to either D2 or D1 receptors
- Risperidone
  - about equally potent in blocking D2 and 5-HT2 receptors
- Olanzapine
  - more potent as an antagonist of 5-HT2 receptors
  - lesser potency at D1, D2, and α1 receptors
- Quetiapine
  - lower-potency compound with relatively similar antagonism of 5-HT2, D2, α1, and α2 receptors

Atypical antipsychotics

- lower doses
- reduced side effects
- more effective (especially negative symptoms)
- better compliance

- Evidence?
  - trials have been quite small and involved patients previously heavily treated and somewhat 'resistant'
  - trials have tended to show equivalent efficacy and better side effect profiles with newer drugs
  - head to head trials claimed superiority of olanzapine over risperidone (but company sponsored and controversial); some "parallel publications"
- Costs
  - Much higher with new drugs (10-40 times higher)

Metabolic effects

Weight gain over 1 year (kg)	
aripiprazole	1
amisulpride	1.5
quetiapine	2 – 3
risperidone	2 – 3
olanzapine	> 6
clozapine	> 6

Insulin resistance

- Prediabetes (impaired fasting glycaemia) has ~ 10% chance / year of converting to Type 2 diabetes
- Prediabetes plus olanzapine has a 6-fold increased risk of conversion
- If olanzapine is stopped 70% will revert back to prediabetes

Stroke in the elderly

- Risperidone and olanzapine associated with increased risk of stroke when used for behavioural control in dementia
- Risperidone 3.3% *vs* 1.2% for placebo
- Olanzapine 1.3% *vs* 0.4% for placebo
- However, large observational database studies
  - Show no increased risk of stroke compared with typical antipsychotics or untreated dementia patients

Conclusions

- Atypical antipsychotics have serotonin blocking effects as well as dopamine blockade
- As a group have less chance of extrapyramidal side effects
- Most have weight gain and insulin resistance as a side effect (except perhaps aripiprazole and maybe amisulpride)
- May be associated with stroke when used for behavioural control in dementia (?!)
- Many have idiosyncratic toxicities

Atypical antipsychotics

- Properties
  - Available evidence to show advantage for some (clozapine, risperidone, olanzapine) but not all atypicals when compared with typicals
  - At least as effective as typicals for positive symptoms
  - May be more efficacious for negative and cognitive symptoms (still under debate)

Atypical antipsychotics

- Potency
  - All atypical antipsychotics are equally effective at therapeutic doses
    - Except clozapine
    - Most effective antipsychotic
    - For resistant schizophrenia
    - 2nd line due to life-threatening side effect

Atypical antipsychotics

Relative incidence of Adverse effects							
Drugs	Sedation	EPS	Anticholinergic	Orthostasis	Seizure	Prolactin elevation	Weight gain
Clozapine	++++	+	++++	++++	++++	0	++++
Risperidone	+++	+	++	+++	++	0 to ++++	++
Olanzapine	+++	+	+++	++	++	+	+++
Quetiapine	+++	+	++	++	++	0	++
Ziprasidone	++	+	++	++	++	0	+
Aripiprazole	++	+	++	++	++	0	+

Atypical antipsychotics

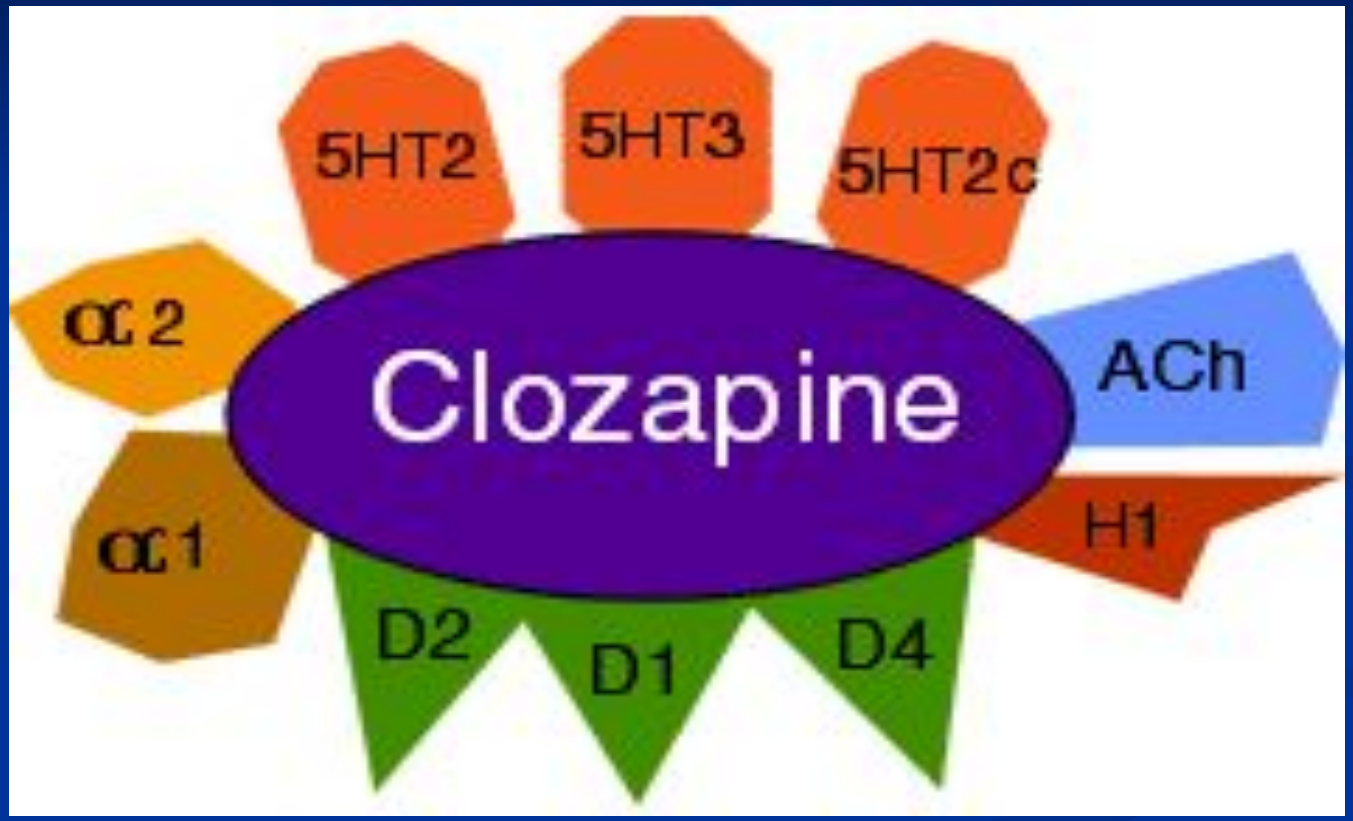
- 1st line atypical antipsychotics
  - All atypicals except clozapine
  - NICE recommendations
    - Atypical antipsychotics considered when choosing 1st line treatment of newly diagnosed schizophrenia
    - Treatment option of choice for managing acute schizophrenic episode
    - Considered when suffering unacceptable adverse effects from a conventional antipsychotic
    - Changing to an atypical not necessary if typical controls symptoms adequately and no unacceptable adverse effects

Atypical antipsychotics

- 2nd line atypical antipsychotic
  - Clozapine
    - Most effective antipsychotic for reducing symptoms and preventing relapse
    - Use of clozapine effectively reduce suicide risk
    - 1% risk of potentially fatal agranulocytosis
      - **Acute pronounced leukopenia with great reduction in number of neutrophil**
  - NICE (The National Institute for Health and Care Excellence) recommendations
    - Clozapine should be introduced if schizophrenia is inadequately controlled despite sequential use of 2 or more antipsychotic (one of which should be an atypical) each for at least 6-8 weeks)

ARRIVAL OF THE ATYPICAL ANTIPSYCHOTIC

- "German psychiatrists working with G. Stille at Wander Pharmaceuticals in Bern, Switzerland, in the early 1960s worked to refute that EPS and antipsychotic efficacy were linked.
- Their work led to the introduction of Clozapine, an antipsychotic with no EPS."
- Clozapine was briefly marketed and quickly withdrawn for two reasons:
  - The embarrassment of not having any EPS, and
  - **Agranulocytosis**

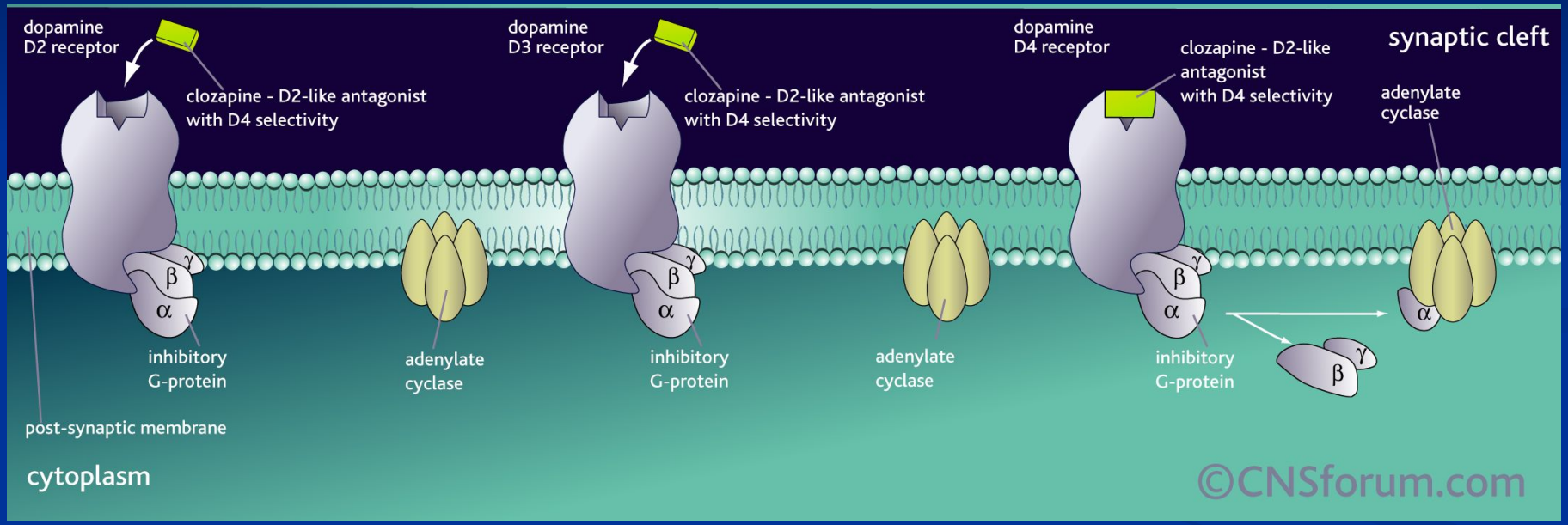

5HT2
5HT3
5HT2c
α2
Clozapine
ACh
α1
H1
D2
D1
D4

NEUROBIOLOGY OF CLOZAPINE

- All schizophrenic patients do not respond to antipsychotics that have an affinity for DA D_2 receptors. This has lead researchers to believe that there are other Dopamine receptors that may contribute to the cause of schizophrenia.
- The DA D_4 subtype has also been implicated in the illness.
- The DA D_4 is of special interest because of its concentration in the hippocampus and the cerebral cortex. It is through the D_2 and the D_4 receptors that Clozapine exerts its affects.

Heinrichs, R. W., (2001). In Search of Madness: Schizophrenia and Neuroscience. Oxford University Press: New York.

NEUROBIOLOGY OF CLOZAPINE



Here you can see that Clozapine will not bind to any Dopamine receptor, it is selective, it has an affinity for the D_4 receptor subtype.

Mechanism of Action

- The exact mechanism of action unknown, however, it is believed that Clozapine selectively antagonizes dopamine D1 and D4 receptors, serotonin 5-HT2 receptors and others.
- Atypical antipsychotics, like Clozapine, are distinguished by their relatively low affinity for the DA D_2 receptor subtype and its high affinity for the DA D_4 receptor subtype and the 5-HT_2 receptor subtype.
- Clozapine may be able to permit more normal dopaminergic function in the anterior pituitary, the mesostriatal, mesolimbic and mesocortical regions

Dosages and Treatment Length

- The regular dosage given to patients is approximately 900mg per day, but the regular range 400-600 mg/d .
- To minimize side effects, the initial dose of Clozapine may start of low and progressively increase to 200mg taken three times per day.
- Clozapine is not a cure for schizophrenia, rather, it is used to relieve the symptoms of the disease. Therefore, the use of anti-psychotics is life-long to ensure that the symptoms are controlled.
- The patient may decide to discontinue the use of Clozapine due to its side effects and is usually placed on a less potent antipsychotic.
- The discontinuation of all anti-psychotics will cause a relapse of positive and negative symptoms.

Atypical antipsychotics

- Clozapine
  - BNF (British National Formulary) 52 (September 2006)
    - Leucocyte and differential blood count normal before starting
    - Monitor counts week for 18 weeks, then at least 2 weeks after 1 year
    - At least 4 weeks after count stable for 1 year (for 4 more weeks after discontinuation)
    - If leucocyte count < 3000/mm3, or if ANC (Absolute Neutrophil Count) < 1500/mm3, discontinue immediately and refer to hematologist
    - Patient should report immediately symptoms of infection, esp. flu-like illness (fever, sore throat)

Atypical antipsychotics

- Clozapine
  - Rare cases of myocarditis and cardiomyopathy
    - Fatal
    - Most commonly in first 2 months
    - CSM (Committee on Safety of Medicines (recommendations
      - Physical exam and medical history before starting
      - Persistent tachycardia esp. in first 2 weeks should prompt observation for cardiomyopathy
      - If myocarditis or cardiomyopathy, stop clozapine
      - Inform patients for unexplained fatigue, dyspnea, tachypnea, chest pain, paipitation and ask them to report these signs and symptoms immediately

Atypical antipsychotics

- Clozapine
  - Contraindication
    - History of clozapine-induced agranulocytosis
    - Bone marrow suppression
    - On myelosuppressive drugs
  - Caution
    - Seizure disorders
    - Diabetes

Dopamine Receptors and Clozapine

•Equivalent occupancy of dopamine D1 and D2 receptors with clozapine: differentiation from other atypical antipsychotics. Am J Psychiatry. 2004 Sep;161(9):1620-5

•Tauscher J, Hussain T, Agid O, Verhoeff NP, Wilson AA, Houle S, Remington G, Zipursky RB, Kapur S.

•OBJECTIVE: Clozapine, the prototype of atypical antipsychotics, remains unique in its efficacy in the treatment of refractory schizophrenia. Its affinity for dopamine D(4) receptors, serotonin 5-HT(2A) receptor antagonism, effects on the noradrenergic system, and its relatively moderate occupancy of D(2) receptors are unlikely to be the critical mechanism underlying its efficacy. In an attempt to elucidate the molecular/synaptic mechanism underlying clozapine's distinctiveness in refractory schizophrenia, the authors studied the in vivo D(1) and D(2) receptor profile of clozapine compared with other atypical antipsychotics.

•RESULTS: The ratio of striatal D(1)/D(2) occupancy was significantly higher for clozapine (0.88) relative to olanzapine (0.54), quetiapine (0.41), or risperidone (0.31).

•CONCLUSIONS: Among the atypical antipsychotics, clozapine appears to have a simultaneous and equivalent occupancy of dopamine D(1) and D(2) receptors. Whether its effect on D(1) receptors represents agonism or antagonism is not yet clear, as this issue is still unresolved in the preclinical arena. This distinctive effect on D(1)/D(2) receptors may be responsible for clozapine's unique effectiveness in patients with schizophrenia refractory to other typical and atypical antipsychotics.

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CLOZAPINE

ADVANTAGES

- Clozapine is considered by many as the only atypical antipsychotic due to its elevated effects over other "atypical" antipsychotics.
- Patients do not experience extrapyramidal symptoms (EPS)
- Used for treatment-resistant patients that have not responded to any other medication.
- Has been shown to have some effectiveness in the treatment of negative symptoms.

DISADVANTAGES

- There is a high correlation between patients who take this medication and the development of Agranulocytosis.
- Clozapine costs more than typical anti-psychotics, however, the cost is relatively the same for atypical antipsychotics
- The effective dose of Clozapine is higher than other atypical antipsychotics.
- Tends to work more effectively in younger patients (20s) than older patients (30s).

CONCLUSIONS

- Is there any controversy involved in using this treatment?
  - There is some controversy surrounding this drug.
  - The debate is over when this drug should be used. Many say that due to the increased risk of attaining Agranulocytosis (which can be fatal is not detected) this drug should be used only if the individual is un responsive to other drugs. However, there has been findings that Clozapine is significantly more affective if administered to the patient at a younger age.
- Is this treatment appropriate for every patient?
  - No
  - Typically Clozapine is used on schizophrenic patients that are treatment-refractory or unresponsive to other medications.

Antipsychotic oral-dispersible and solution preparations

- Oral-dispersible preps available for
  - 2 atypicals
    - Risperidone (Risperdal Quicklet®)
    - Olanzapine (Zyprexa Zydis®)
  - Carefully peel off packing, allow tablet to dissolve on tongue and swallow
  - Do not break the tablet
  - Some may be dispersed in fluids (consult manufacturer literature)
- Solutions available for
  - 1 typical
    - Haloperidol (Haldol® drops)
  - 1 atypical
    - Risperidone (Risperdal® solution)
  - Very concentrated, avoid from contact with skin (dermatitis)

Antipsychotic depot injections

- Available for
  - 4 typicals
    - Haloperidol decanoate (Haldol Decanoate®)
    - Fluphenazine decanoate (Modecate®)
    - Flupenthixol (Fluanxol®)
    - Zuclopenthixol (Clopixol Depot®)
  - 3 atypical
    - Risperidone (Risperdal Consta®)
    - Zyprexa (Zypadhera®)
    - Xeplion (Aripiprizol ®)
  - Used for chronic illness and history of noncompliance
  - Trial of oral meds first to assess tolerability

Antipsychotics in schizophrenia

- Selection of typical antipsychotics
  - Equally efficacious
  - Chosen by side effect profile
- Atypical antipsychotics may be appropriate if
  - Adverse effect is a particular concern
  - Additional benefits for negative and cognitive symptoms required
- Clozapine
  - 2nd line treatment when other agents are ineffective or not tolerated

Antipsychotics in schizophrenia

- Treatment response
  - First 7 days
    - Decreased agitation, hostility, combativeness, anxiety, tension and aggression
    - Normalization of sleep and eating habits
  - First 2-3 weeks
    - Increased socialization, improvement in self-care
  - 6-8 weeks
    - Improvement in formal thought disorder

ГУ «РЕСПУБЛИКАНСКИЙ НАУЧНО-ПРАКТИЧЕСКИЙ ЦЕНТР ПСИХИЧЕСКОГО ЗДОРОВЬЯ»

Выписка из истории болезни № 241

[redacted] **АЛЕКСАНДР МИХАЙЛОВИЧ, 10.07.1992 г.р.**

[redacted]

не работает

Дата поступления: 06.01.14 г. **Дата выписки**: 18.02.14 г.

Д-з: Острый шизофреноподобной психоз вследствие употребления амфетаминов. F 15.50

Лечение: галоперидол, трифтазин, клопиксол-акуфаз, модитен-депо, клозапин, циклодол, депакин, диазепам, витамины.

СОМАТИЧЕСКИ: Кожные покровы обычной окраски. Телосложение правильное. Тоны сердца ритмичные, АД 120/80 мм.рт.ст. Дыхание везикулярное, хрипов нет. Живот мягкий б/бол. Стул, диурез без особенностей.

НЕВРОЛОГИЧЕСКИ: Зрачки равновеликие, оскал симметричен, язык по средней линии, движения в конечностях сохранены в полном объеме. Парезов нет, походка обычная. Менингиальных симптомов нет.

КОНСУЛЬТАЦИИ СПЕЦИАЛИСТОВ:

Консультация доц. [redacted]. от 13.02.14 г. – д-з: Острый шизофреноподобной психоз вследствие употребления амфетаминов.

Психологич. иссл.: проявление импульсивности, формальности, единичные признаки растерянности и аутичности; легкие орг. знаки; фобические и враждебные тенденции.

ЭКГ от 13.01.14 г.: синусовый ритм, ЧСС 93 уд/мин. Вертикальное положение ЭОС. Тахисистолия. НПР в нижней области ЛЖ.

ЭЭГ от 13.01.14 г.: Диффузные изменения корковой ритмики ирритативного характера в виде альфа-бета-волновой дизритмии с признаками усиления бета-активности и немногочисленными вспышками невысоких, билатерально-синхронных острых волн. Возможна дисфункция неспецифических срединных и стволовых структур мозга.

ЛАБОРАТОРНО:

Общий анализ крови от 08.01.14 г.: лейк. – 4,6; эритроциты – 4,83; гемоглобин-152, СОЭ – 3 мм/час.

Биохим. анализ крови от 09.01.14 г.: АСТ – 71 ед/л.; АЛТ – 36 ед/л.; бил.– 6,6 мкмоль/л, глюкоза- 3,8

ИФА АНТИ ЛЮЭС от 09.01.14 г. № 561 - отрицательная.

Анализ мочи от 09.01.14 г.: норма. Микробов кишечной группы не найдено.

ПСИХИЧЕСКИ: Сознание ясное. Ориентирован полностью. Осмотрен после медикаментозного сна. Сообщил, что при поступлении был тревожен, слышал голоса в голове, боялся всего вокруг, было чувство, что кто-то преследует, не спал. На момент осмотра внешне опрятен.. Жесты, мимика выразительные. Контактен. Настроение снижено. отмечает путаницу в голове в последние 2 месяца. Критика формальная. Вне агрессивных, суицидальных тенденций.

18.02.14 г. представлен ВКК в связи с выпиской – д-з: Острый шизофреноподобной психоз вследствие употребления амфетаминов. F 15.50.

За время лечения купированы психотические симптомы, нормализован ночной сон, сформирована установка на отказ от ПАВ. Пациент Выписан в сопровождении родственников.

Рекомендовано:

1. модитен-депо 1,0 м/м 1 р/мес (введен 12.02.14 г.);
2. клозапин 25 мг днём, 50 мг вечером;
3. депокин-хроно 300 мг 2 р/д;
4. циклодол 2 мг утром и днем при треморе, скованности.

Выписка – в [redacted]

Врач: [redacted]

Зав. отд.: [redacted]

Antipsychotics in schizophrenia

- Acute phase
  - Initiate therapy
  - Titrate as tolerated to average effective dose
- Stabilization phase
  - Dose titration within the therapeutic range
- Maintenance phase
  - Therapy should be continued for at least 12 months after remission of 1st episode
  - Good treatment responders should be treated for at least 5 years
  - Continuous lifetime maintenance required in the majority of patients to prevent relapse
    - **Lowest effective and tolerable dose**

Non-antipsychotic agents

- Benzodiazepines
  - Useful in some studies for anxiety, agitation, global impairment and psychosis
  - Schizophrenic patients are prone to BZD abuse
  - Limit use to short trials (2-4 weeks) for management of severe agitation and anxiety
- Lithium
  - Limited role in schizophrenia monotherapy
  - Improve psychosis, depression, excitement, and irritability when used with antipsychotic in some studies

Non-antipsychotic agents

- Carbamazepine
  - Weak support when used alone and with antipsychotic
  - Alters metabolism of antipsychotic
  - NOT to be used with clozapine (risk of agranulocytosis)
- Valproate
  - Concurrent administration with risperidone and olanzapine resulted in early psychotic improvement in recent investigation
- Propranolol
  - Research showed improvement in chronic aggression
  - Treat aggression or enhance antipsychotic response
  - Reasonable trial −240mg/day

Pregnancy and antipsychotics

Atypical	Most data for olanzapine
Typical	NOT CPZ: sl. Data for malformations

Cytochrome p450* & psychotropes

Time course	Induction: takes weeks Inhibition: 2-3 days → toxicity	
Substrates	↓ *Inhibitor*	↑ *inducers*
Antidepressants Anticonvulsants Methadone/bup BDZ & zop's OLZ/Risp Zuclo Thioridazine Pimozide	Fluoxetine Fluvoxamine Sertraline Paroxetine Clomipramine Haloperidol Thioridazine Methadone	Barbiturates Carbamazepine St John's Wort Cigarettes

Thank you for your attention!