Olanzapine
Its Use in Palliative care and Medicine

- *“ The Wonder drug”?*

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- *UVA*

- **Declaration of interests**
- There are no conflicts of interest declared.

Objectives:

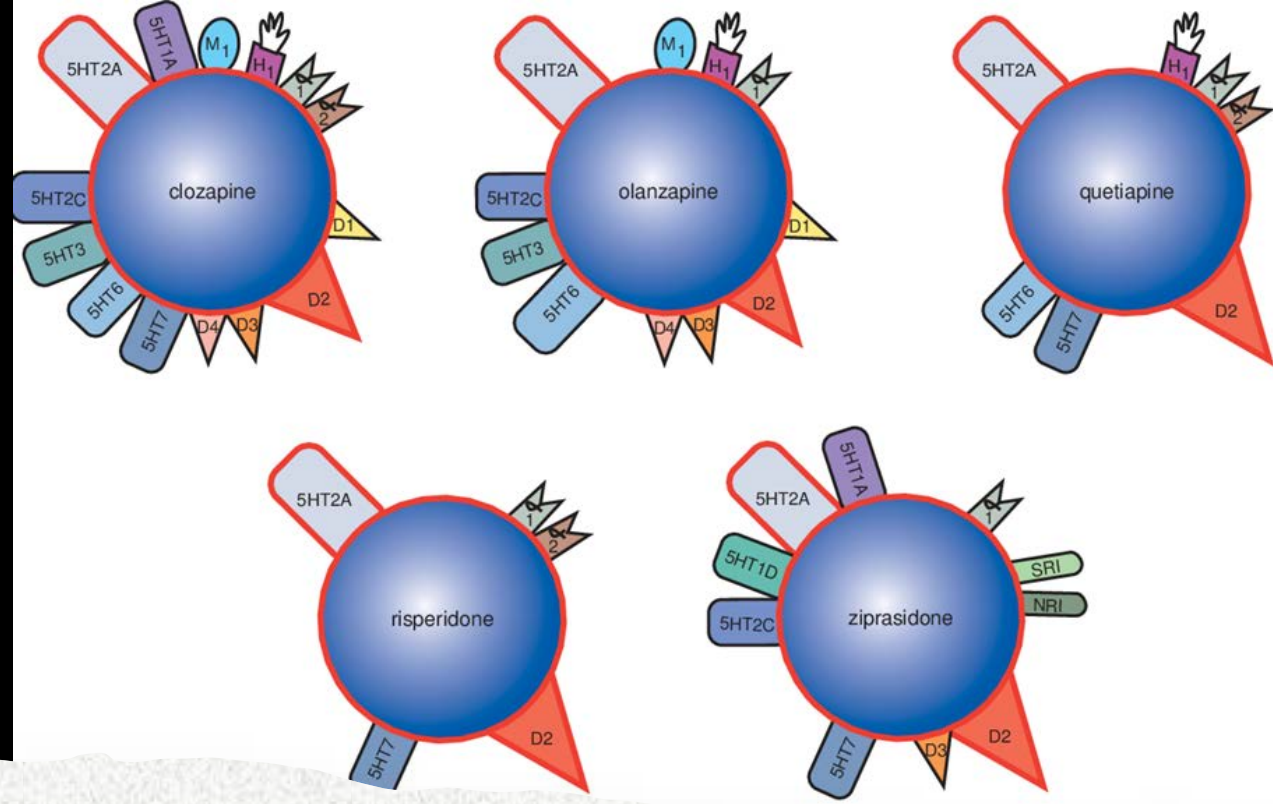
- Understand the Mechanism of Olanzapine.
- Understand Pharmacology/Pharmacodynamics of Olanzapine and how it relates to its uses and side effect profile.
- Understanding interactions of Different receptors with Olanzapine and relations to its use in Palliative care and Managing Symptoms
- Theory of Olanzapine for possible use in Addiction Treatment.

Olanzapine

- is an antipsychotic drug
- Olanzapine is a thienobenzodiazepine classified as an atypical or second-generation antipsychotic agent.
- Quickly gained traction for its reduced side effects.

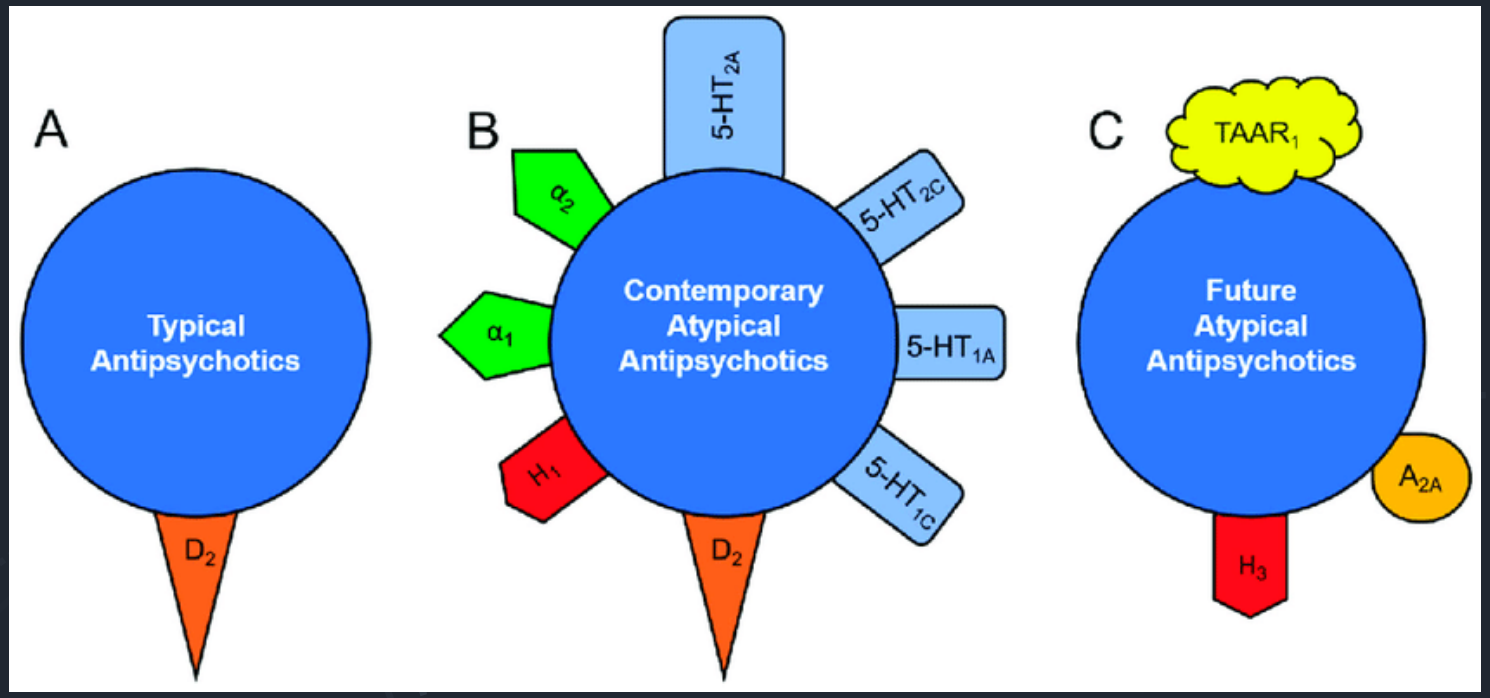
Indications:

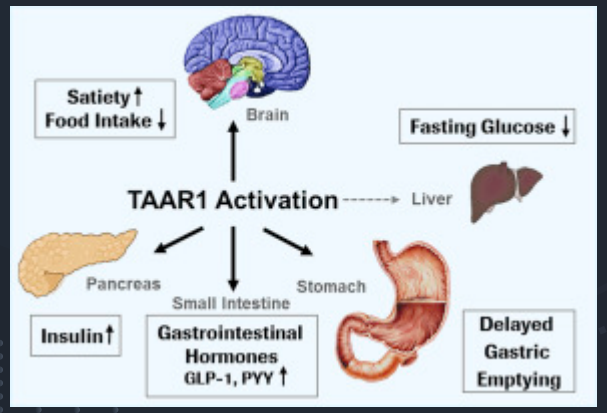
- Psychiatric disorders such as bipolar I disorder including mixed or manic episodes.
- Episodes of depression associated with bipolar disorder type 1 and treatment-resistant depression.
- Psychomotor agitation associated with schizophrenia and bipolar I mania.



Mechanism of action

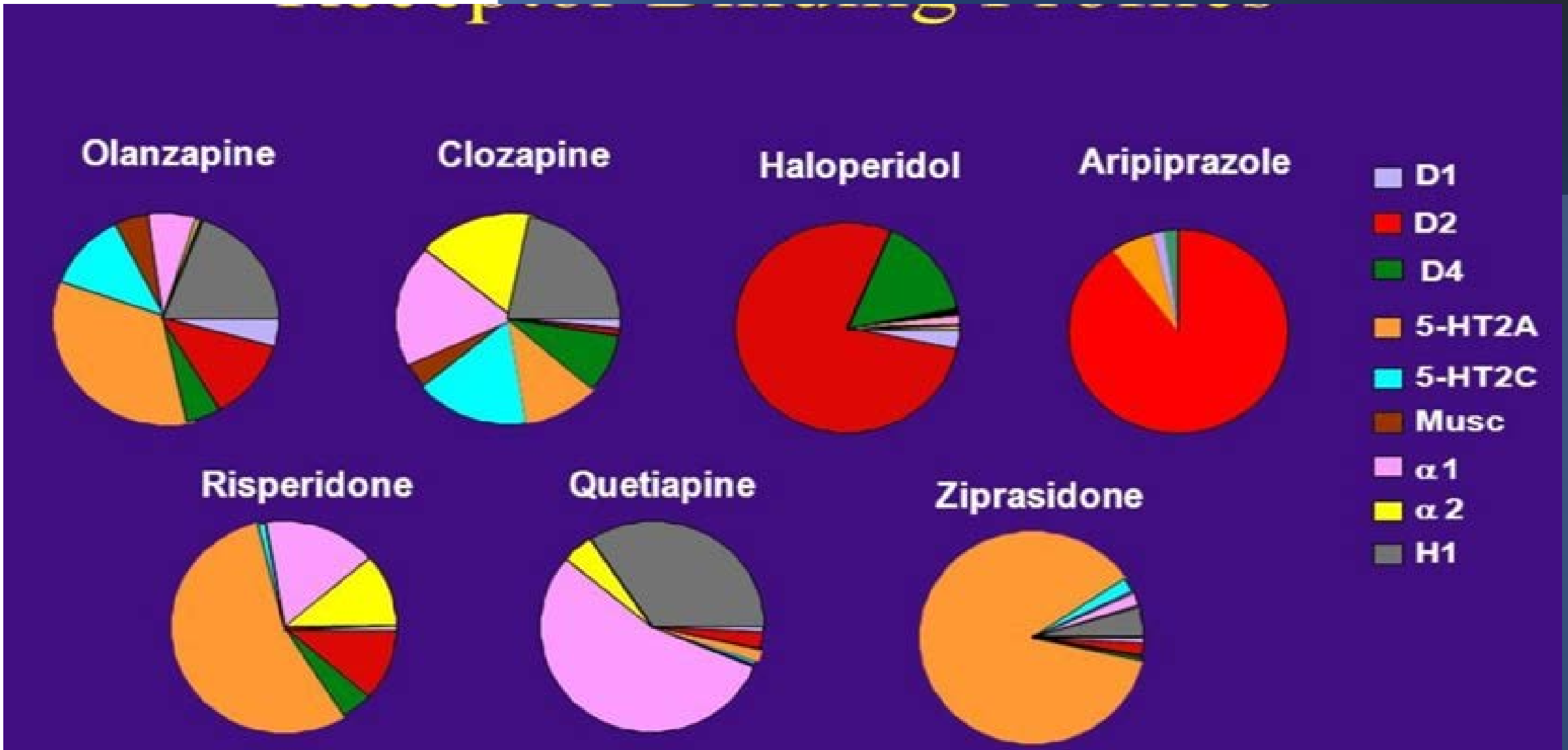
- **The antagonism activity**
- Its **antagonistic effect** towards the dopamine D2 receptor in the mesolimbic pathway.

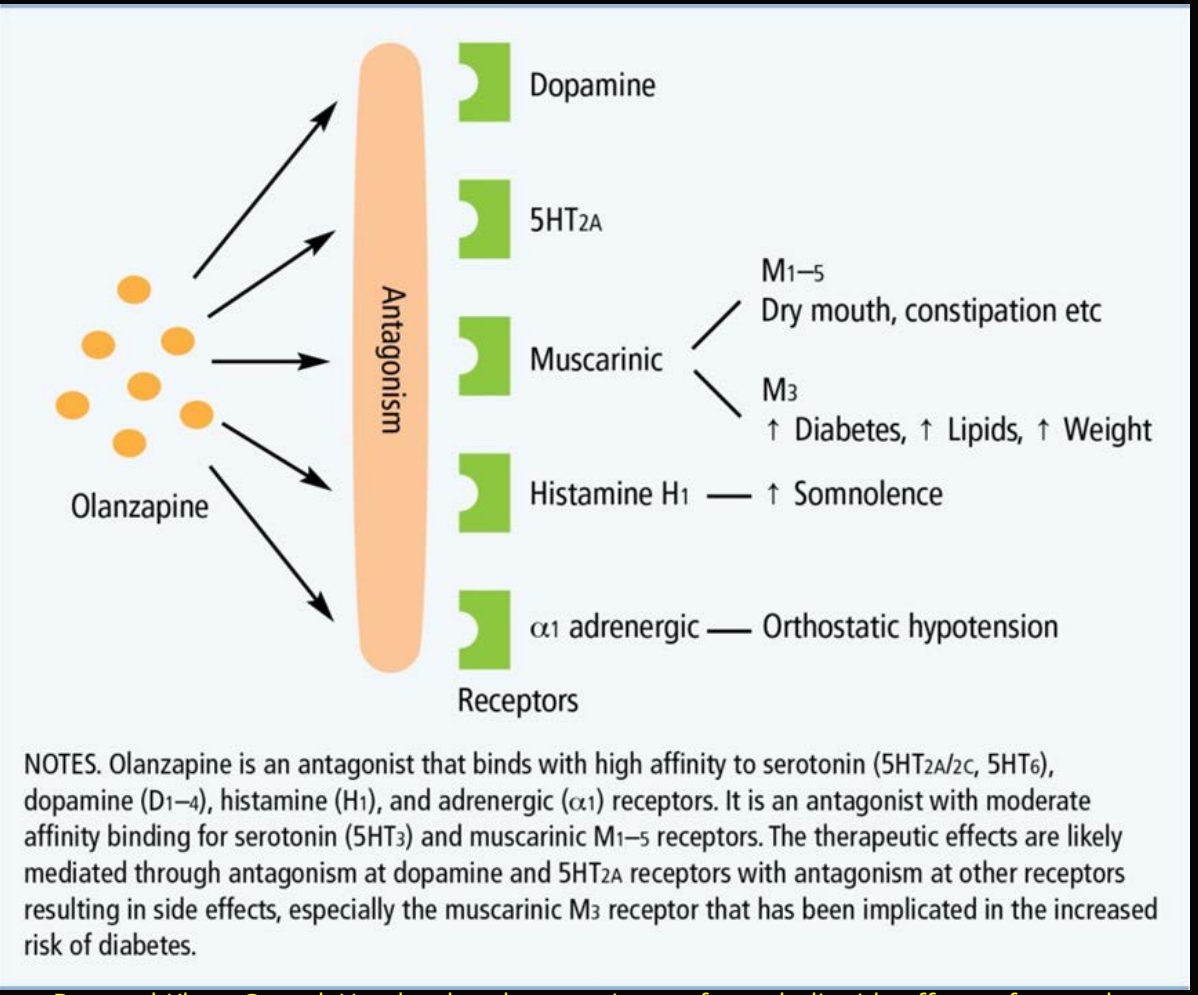




Trace amine-associated receptor-1 (TAAR1),

- https://www.researchgate.net/figure/Receptor-binding-profile-of-antipsychotic-drugs-Typical-antipsychotics-A-act-almost_fig1_347638619


Olanzapine
Clozapine
Haloperidol
Aripiprazole
Risperidone
Quetiapine
Ziprasidone
D1
D2
D4
5-HT2A
5-HT2C
Musc
α1
α2
H1



NOTES. Olanzapine is an antagonist that binds with high affinity to serotonin (5HT2A/2C, 5HT6), dopamine (D1–4), histamine (H1), and adrenergic (α1) receptors. It is an antagonist with moderate affinity binding for serotonin (5HT3) and muscarinic M1–5 receptors. The therapeutic effects are likely mediated through antagonism at dopamine and 5HT2A receptors with antagonism at other receptors resulting in side effects, especially the muscarinic M3 receptor that has been implicated in the increased risk of diabetes.

- Olanzapine has a unique receptor profile amongst antipsychotics, which in part accounts for its various uses and side effects.
- In addition to antagonizing dopamine receptors in the CNS (nausea, delirium), it blocks serotonin (5HT2) receptors (insomnia, anxiety, cachexia) and is anticholinergic.
- It reaches its peak concentration in ~6 hours but has a terminal half-life between 21 to 54 hours.

Rummel-Kluge C, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2010; **123**(2–3): 225– 33

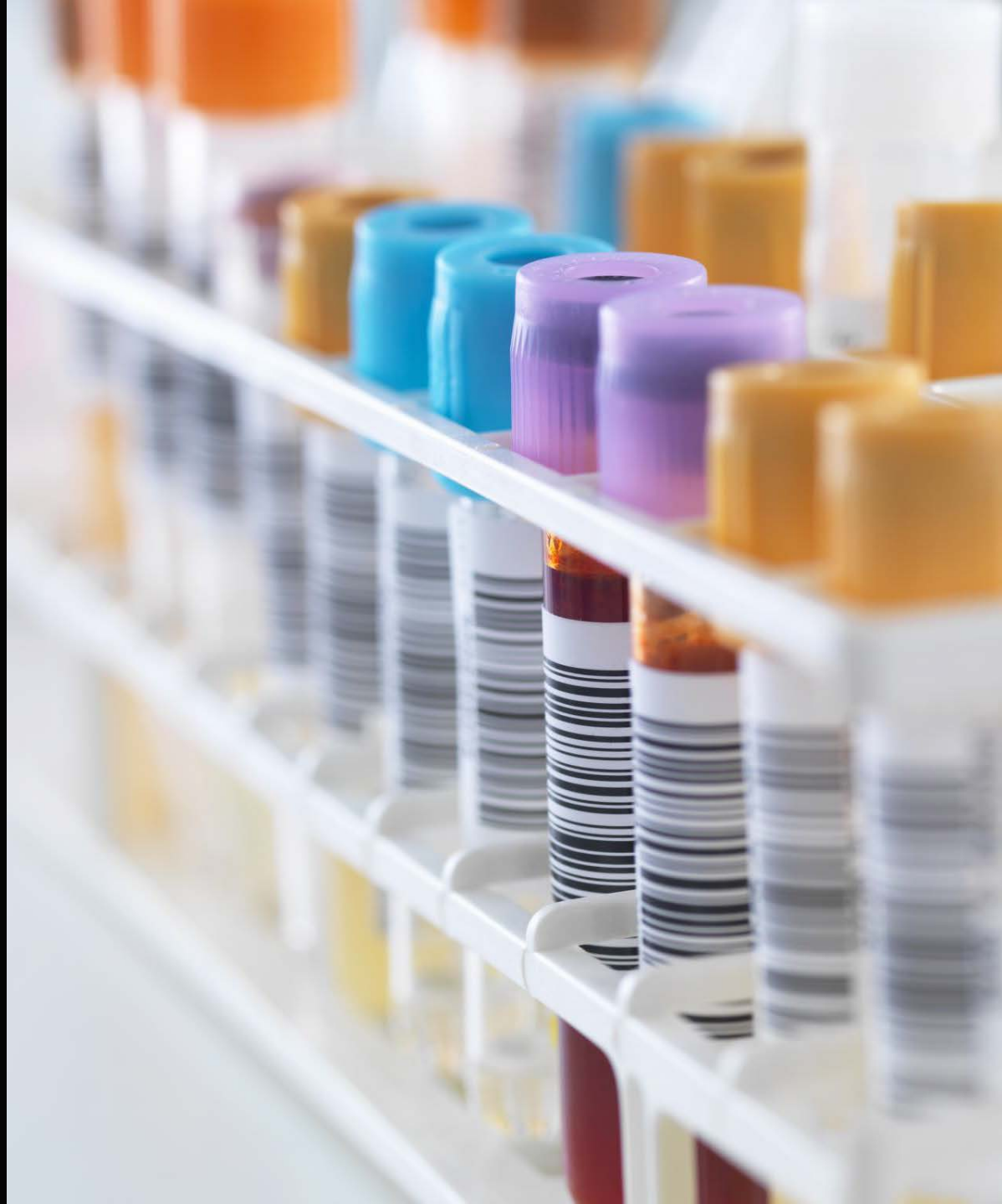
Pharmacodynamics

- The effect of olanzapine in the D2 receptor is reported to produce the positive effects of this drug such as a decrease in hallucinations, delusions, disorganized speech, disorganized thought, and disorganized behavior.
- its effect on the serotonin 5HT2A receptor prevents the onset of anhedonia, flat affect, alogia, avolition and poor attention.
- The effect of olanzapine on dopamine and serotonin receptors has been suggested to reduce chemotherapy-induced nausea and vomiting

PROS AND CONS

When compared to other antipsychotics,

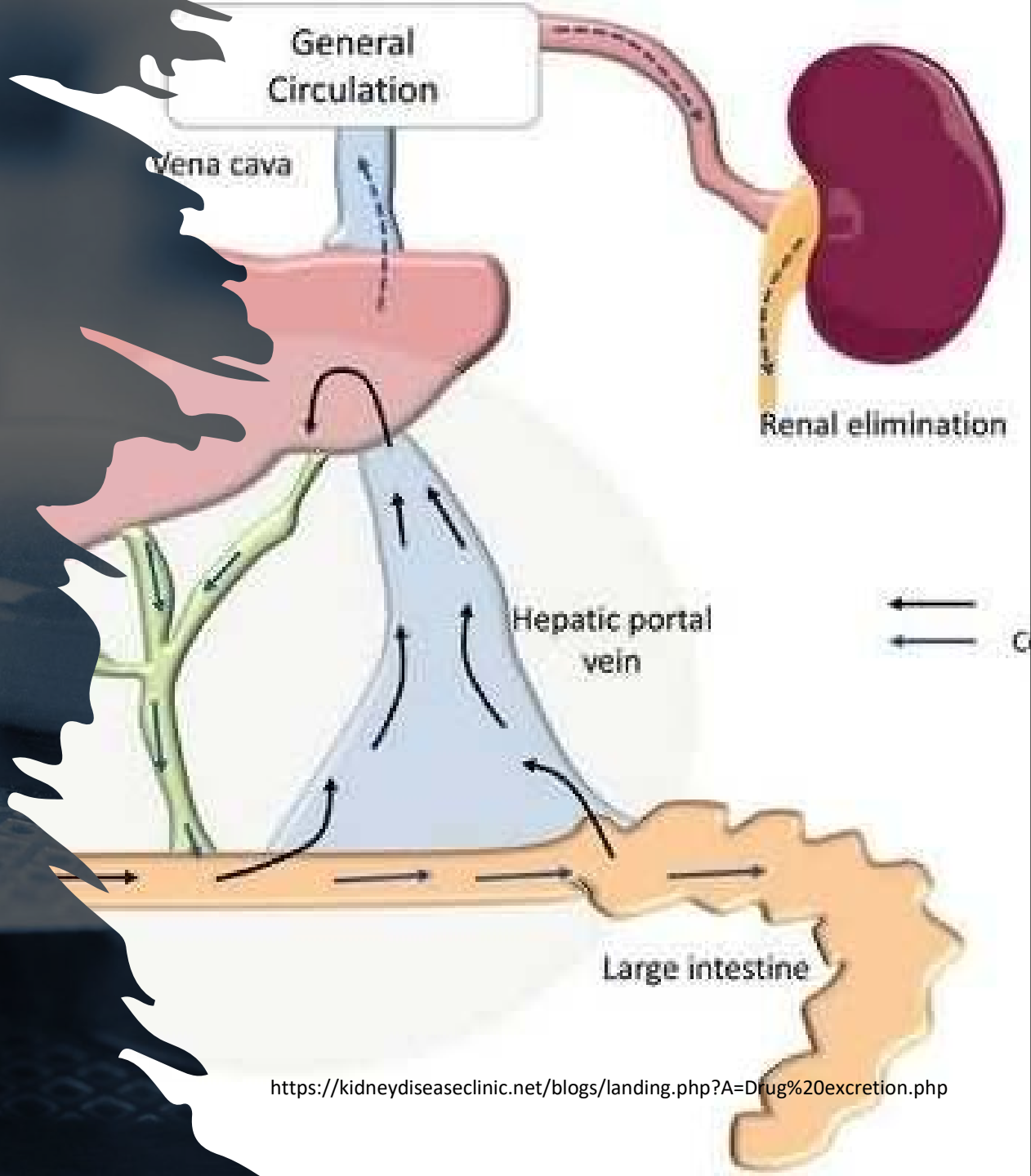
1) Olanzapine causes fewer extrapyramidal symptoms
2) Lesser effect on the QTc interval compared to IV haloperidol
3) It may have a higher prevalence of somnolence and weight gain. (Weight gain is even more apparent in children than adults).
4) Olanzapine has been associated with dry mouth, hyperglycemia, edema, and an increased mortality in elderly patients with dementia-related psychosis.
5) No dosage adjustments are required for patients with renal or hepatic impairment, although caution is recommended in end stage liver disease.



Route of Elimination:

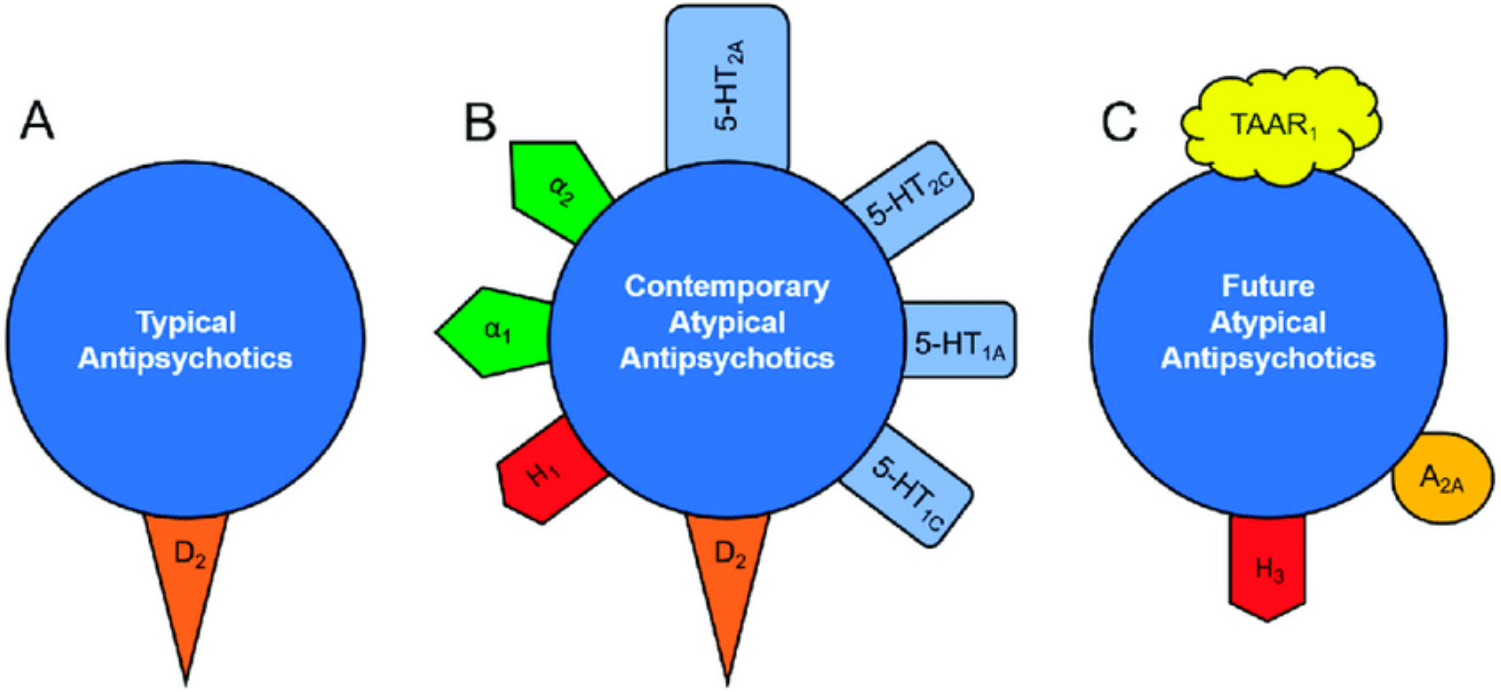
Olanzapine is mainly eliminated through metabolism and hence, only 7% of the eliminated drug can be found as the unchanged form.

- It is mainly excreted in the urine which represents around 53% of the excreted dose followed by the feces that represent about 30%



https://kidneydiseaseclinic.net/blogs/landing.php?A=Drug%20excretion.php

Palliative Care and its Management



Nausea:

- Two small case series and a retrospective study described the effective use of olanzapine (average dose of 5 mg per day) for chronic nausea and vomiting related to an incomplete bowel obstruction.

- In an open-label pilot study, advanced cancer patients receiving olanzapine at doses between 2.5 to 10 mg had a significant improvement in quality of life and a decrease in nausea compared to baseline.

CINV (Chemotherapy induced Nausea and Vomiting)

- There is more robust evidence to support its efficacy in the treatment of chemotherapy-induced nausea and vomiting (CINV).

- A double blinded randomized controlled trial of breakthrough CINV showed benefit of olanzapine compared to metoclopramide (no emesis, 70% vs 31%) with a number-needed-to-treat of 2.5 .

Delirium:

- Doses typically range from 2.5 to 10 mg daily but can reach a maximum of 20 mg daily .
- An open-label preliminary trial studied the tolerability of subcutaneous olanzapine for delirious patients with advanced cancer — 37% of the patients responded to olanzapine at doses 5 mg or 10 mg .
- In another open-label prospective trial, 79 hospitalized cancer patients with delirium were treated with olanzapine and 76% had complete reversal of delirium.

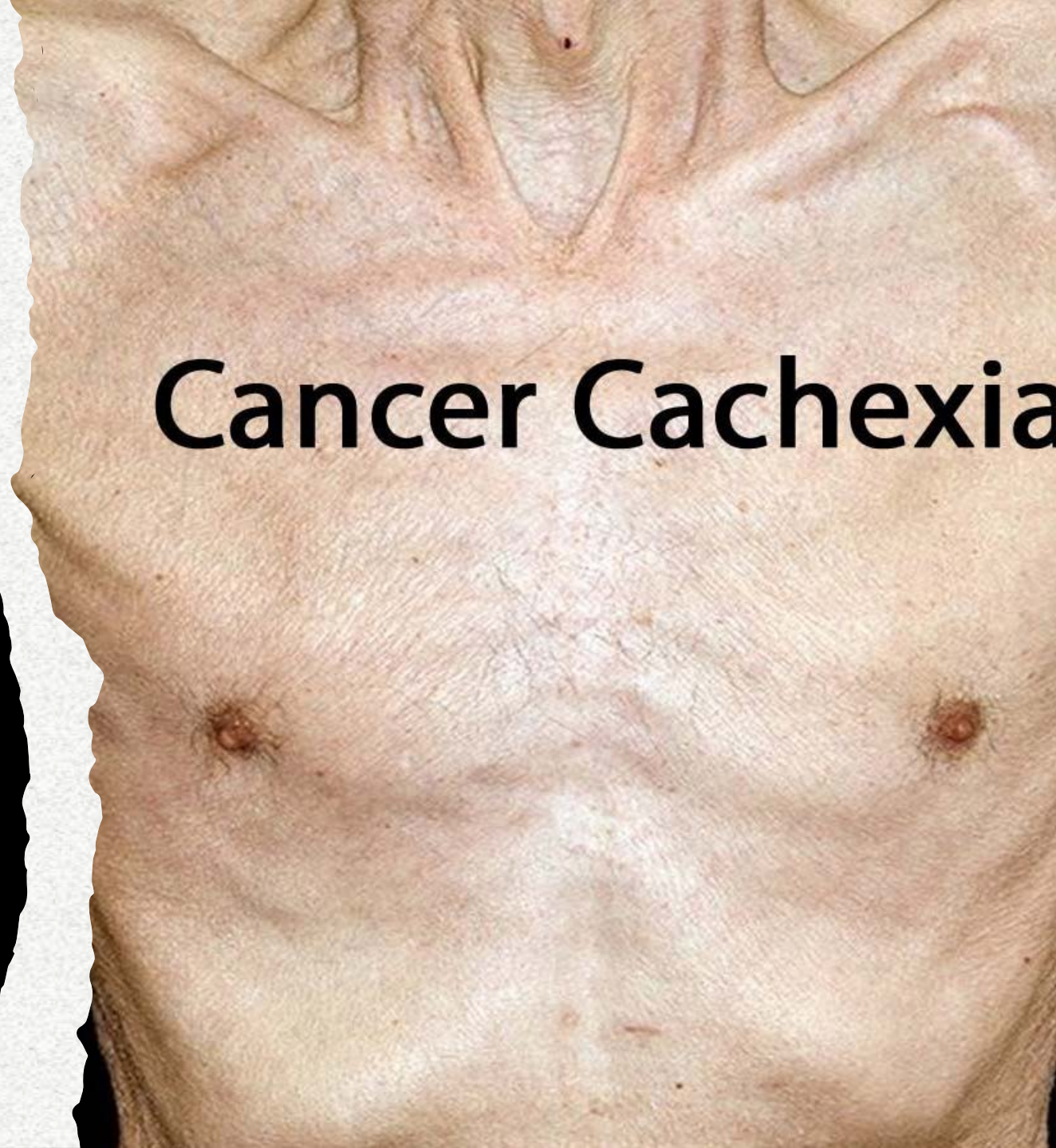
- **Anxiety:** Olanzapine (mean dose 8.7 mg/day) was better than placebo when added to GAD therapy

- **Insomnia**: Olanzapine has been shown to improve sleep efficiency and sleep quality when combined with an SSRI in depressed patients starting with as little as 2.5 mg.

- Improve total sleep time and/or sleep efficiency in healthy subjects and schizophrenic patients.

- **Cachexia**: Olanzapine has been studied for use in cachexia related to chronic illnesses like cancer.

- In an open-label study, olanzapine at doses of 2.5 to 20 mg attenuated the weight loss of advanced cancer patients when used as monotherapy.



Psych

- **Corticosteroid-Induced Psychiatric Symptoms** olanzapine (2.5-20 mg/day) may lead to symptom resolution within days to weeks.

- Olanzapine (5 mg) have both been shown to reduce nightmares in small pilot studies of patients with acute stress and PTSD, including reduction in flashbacks, hyperarousal, and disturbed sleep.

Cost:

- Oral tablets ten times the cost of metoclopramide, fifteen times the cost of trazodone and 30 times the cost of haloperidol.

- Oral disintegrating tablet (ODT) and an intramuscular injection are also available. Low dose the same price, higher dose, increase cost.

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Recap:

- Olanzapine activity with different Dopamine and serotonin receptors makes it a drug of choice for many Palliative symptom Management.
- It Helps with Management of following symptoms:

1)Nausea, CIMV

2) Appetite Stimulant, Cancer Cachexia

3) Delirium , Steroid induced Pyschosis

4) Anxiety

5) Insomnia, Nightmares

6) Addiction treatment???

Olanzapine and Addiction treatment

Idea of using it as an addiction treatment

Theory: Addiction Management Use

- Olanzapine has been reported to reduce cravings and consumption in alcohol-addicted patients.
- Given the common mechanism for opioid addiction, olanzapine may be a useful treatment for opioid-addicted cancer patients.
- Efficacy of olanzapine in reducing the cravings of noncancer patients for alcohol, heroin, and maybe cocaine.

The Mechanisms:

- The mesolimbic system.
- Opioids induce a rush of dopamines
- Considering these pathophysiological mechanisms, olanzapine, a dopamine receptor antagonist, may play a role in managing psychological dependence.
- Short-acting opioids including BTFC (buccal tablet of fentanyl citrate) are more likely to cause a patient to develop misuse than are other long-acting opioid analgesics.

Future research is warranted to study the efficacy of olanzapine as a treatment for opioid addition.

Articles on Heroin, Alcohol and Cocaine addictions with Olanzapine:

- Hutchison KE, Ray L, Sandman E, et al.: The effect of olanzapine on craving and alcohol consumption. Neuropsychopharmacology 2006;31:1310–1317.
- Guardia J, Segura L, Gonzalvo B, et al.: A double-blind, placebo-controlled study of olanzapine in the treatment of alcohol-dependence disorder. Alcohol Clin Exp Res 2004; 28:736–745.
- Gerra G, Di Petta G, D'Amore A, et al.: Effects of olanzapine on aggressiveness in heroin dependent patients. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1291–1298.
- Hamilton JD, Nguyen QX, Gerber RM, Rubio NB: Olanzapine in cocaine dependence: A double-blind, placebocontrolled trial. Am J Addict 2009;18:48–52.

Articles in Brief

Hutchison KE, Ray L, Sandman E, et al.: The effect of olanzapine on craving and alcohol consumption. Neuropsychopharmacology 2006;31:1310–1317

- Participants who met DSM IV criteria for alcohol dependence were randomly assigned to receive olanzapine (5 mg) or a placebo over the course of the trial.
- After 2 weeks of treatment, responded to olanzapine with reductions in cue-elicited craving as well as reductions in alcohol consumption over the course of the 12-week trial

Guardia J, Segura L, Gonzalvo B, et al.: A double-blind, placebo-controlled study of olanzapine in the treatment of alcohol-dependence disorder. Alcohol Clin Exp Res 2004; 28:736–745

- A total of 60 alcohol-dependent patients were assigned to 12 weeks' treatment with either olanzapine or placebo.
- Alcohol consumption, craving, adverse events, and changes in the biochemical markers of heavy drinking and possible toxicity were also evaluated.
- Study found no differences in relapse rate or other drinking variables when comparing olanzapine with placebo-treated patients.

An Article: The Use of Olanzapine for Nonmedical Opioid Use in a Patient with Cancer Receiving Palliative Care. JOURNAL OF PALLIATIVE MEDICINE Volume 25, Number 2**, 2022**

- A 65-year-old woman diagnosed with advanced metastatic tongue cancer.
- OUD was reported.
- Started on Olanzapine 2.5mg po daily, increased to 5 mg, and 8 days f/u period, craving behaviors were markedly reduced.

Gerra G, Di Petta G, D'Amore A, et al.: Effects of olanzapine on aggressiveness in heroin dependent patients. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:1291–1298.

- This study compared the anti-aggressiveness effects of the atypical anti-psychotic olanzapine with that of selective serotonin reuptake inhibitors (SSRI) and benzodiazepines (BZD) among patients with heroin dependence submitted to opioid-agonists substitution treatment.
- Sixty-seven (67) patients who met the DSM-IV criteria for heroin dependence and showed aggressive personality traits.
- Study findings suggest that Olanzapine may be useful as an adjunctive agent in reducing aggressive/hostile behaviour in heroin addicted individuals during maintenance substitution treatment. Otherwise, atypical anti-psychotic olanzapine seems to be unable to improve the outcome in terms of addictive behavior and relapse risk in the addicted patients not affected by overt psychotic disorders.

Hamilton JD, Nguyen QX, Gerber RM, Rubio NB: Olanzapine in cocaine dependence: A double-blind, placebocontrolled trial. Am J Addict 2009;18:48–52.

- Study conducted with a randomized, double-blind, placebo-controlled trial in which 48 cocaine-dependent subjects received olanzapine or identical-appearing placebo for 16 weeks.
- The primary outcome measure was the proportion of cocaine-negative weekly urine screens during treatment.
- Secondary measures included scores on a Craving Questionnaire, Addiction Severity Index subscales, and extrapyramidal symptom scales.
- Study concluded that olanzapine appears ineffective for cocaine dependence.

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- Questions and Discussions

THANK YOU!