

OLANZAPINE



"Extraction of the Stone of Madness" (or "The Cure of Folly"), oil on board, 1494, Hieronymus Bosch. Museo del Prado, Madrid.

...Now we shall write the fifth chapter about insane persons and their cure...First we shall speak of the Lunatici; in this cure we prevent the attraction of the Moon by confortativa, so that the Lunatici may offer resistance, like a roof which is put up against the sun, lest what is lying under the sun be disturbed by its existence. First we must bear in mind that the power which the Moon as well as that of all other planets and influences which take strength from our bodies, holds over us, as well as the sun, can be taken away by the power of medicine. The Moon is like a magnet which attracts all iron and steel. The power can be taken away from it as from the iron, for iron that has been covered with oleum mercurii will not be attracted by any magnet, nor will a magnet rubbed in leek ever attract anything. Thus we have to distinguish several medicines to use against the Moon, some against Mars, some against the Sun, some against all planets. Therefore one should try to build up resistance against these influences by medicines which could be applied in correlation with the power of the Moon, or with that of the other planets or stars...Therefore if a planet destroys a corpus, the quintessence of metal should be applied against it. For instance: quintessence solis against the Sun, quintessence lunae against the Moon, etc. it must be understood that quintessence soli is powerful against all planets, because of its specifica and the great power which it gives to the heart, by which all this is driven out, as we say in De Septem Membris and has been reported sufficiently in De Lunaticis.

We also want to describe the treatment for those persons who have brought insanity from the mother's womb as a heritage. There are two cures: one is a preventive for the father and mother, so that insanity may not affect the child; it also is for the insane person himself. This first cure should be performed as follows, and be called rather a preventive or expulsive remedy than a cure: The parents should not perform a natural coitus but an artificial one. When they have the desire for intercourse this insanity is hidden and appears due to coitus, if the coitus has been performed during insanity. It leads to insanity. Then the child will be insane. If, however, no coitus is performed during the illness, but if coitus precedes the illness, the child will not be insane. From this it follows that one should not cohabit when feeling the desire for it, but should immediately jump into cold water; thus the desire for coitus will be expelled or extinguished. When the fervor has been extinguished the coitus should be performed artificially. It can be induced and stimulated by medicine. Then a natural act will follow consistent with nature and not with the spirit or will of insanity. Thus whenever one has the desire for coitus, it should be incited by medicine. It can be seen by this that nature in itself does not produce insanity, but is good. If the insanity is of a permanent nature, then the coitus can be prevented every day in the above described manner, and if the first child is not perfectly free from insanity, his children will be free from it through this method. It should be remembered that insane persons must be protected by quintessence before the coitus. In this way the genital organs are protected against things unsuitable and inconvenient, so that no evil birth or insanity may result.

The second cure is for the insane and is done as follows: through confortativa or through sedatives. The cure is not possible and cannot expel insanity unless the make-up and humors of these persons are changed and redirected, so that the new make-up may be stronger and more powerful than the old. Then nature feels such assistance that all these die away. Confortativa should only be made of quintessence, like quintessence solis, perlarum, argenti, corallorum, antimonii, vitrioli, sophie, etc; and the sedatives should be made like mitigatium magnum, anodinium temperatum, etc.

By these indicated remedies insane persons can and should be completely restored, so that they will not be insane again. There is no other way of fighting the cause of insanity, although there are still many other things which may be used against it, which we shall not enumerate...

*On the Treatment of Versanias, in
“The Diseases that Deprive Man of His Reason, Such as St Vitus’ Dance, Falling Sickness,
Melancholy and Insanity, and their Correct Treatment”.
By Theophrastus Paracelsus, in the Year, Anno Domini, 1597.*

In the long lexicon of the history of Medicine, perhaps none have been so enigmatic nor so controversial as the self taught self proclaimed Swiss Physician, Theophrastus Paracelsus Bombast, von Hohenheim, otherwise known to history as Paracelsus. Born the late Fifteenth century, he lived during the time of the High Renaissance, but he also stood at the very cross roads of the old medieval world and the modern world. He has been counted, by some, as among the founding fathers of modern science, and in some ways he was in his rejection of received classical dogma, preferring to draw his own conclusions from his own observations, and yet at the same time he was deeply religious, and deeply superstitious, believing firmly in archaic elements or even his own inventions of astrology, alchemy and the occult. Ferdinand Hoefer in his “History of Chemistry” written in 1843, has perhaps left us the most penetrating description of this most perplexing man: “...Picture to yourself a man who in certain moments, gives evidence of a remarkable penetration, and in others raves in the most pitiable manner possible; a man who, at one time, devoted to the progress of science, proclaims the absolute authority of experience, and thunders the most violent anathemas against the theories of the ancients; yet at another time, like a lunatic, seems to converse with demons and believe in their absolute power. Fasting in the morning, drunk in the evening, presenting exactly every idea in the order in which it came to his mind, such is Paracelsus...”

*When we look our distant past history to try to understand from where we have come and just exactly how we have arrived to our present state of medical knowledge the picture we see is both deeply fascinating but same the same time quite startling even - disturbing. In Paracelsus’s writings on the treatment of the insane, we see some modern elements such as the hereditability of mental illness, as well as its amenability to treatment by drugs - yet many other elements are positively medieval. Insanity for example can be a result of malignant influences from the Moon, (...perhaps lending some insight into the historical notion that madness is brought out by the full Moon!), or that coitus during a moment of insanity will result in offspring that will suffer from this malady. Drugs of the appropriate “quintessence”, however, are available, he assured us to treat this madness should it occur, by either inherited or acquired means. Modern historians are very quick to assign “genius” when they find ideas consistent with modern knowledge but also just a quick to assign archaic superstition when they do not. But to those of past times these retrospective assessments of course are not a fair or in many ways even a relevant assessment. In the words of the magisterial Philip Ball, “Today we have the luxury of being able to regard astrology and magic as forms of foolishness”. But there was very little of this luxury in the Sixteenth century. Astrology, magic, the occult, alchemy and religion, all held equal validly with what today we would call the scientific method. Our modern science, Philip Ball fascinatingly points out, stemmed not so much from efforts to get rid of them - as to **understand** them!*

Today we understand that acquired mental illness is not a result of malignant astrological influences, as Paracelsus once thought. They can certainly be the result of heredity, though not in quite the way Paracelsus supposed. But in regards to a place for sedative treatment we certainly do agree with Paracelsus - he would have been quite impressed with our modern pharmacological array, an array which includes a powerful “quintessence of sol” - known as Olanzapine.

OLANZAPINE

Introduction

Olanzapine is a second generation (“atypical”) antipsychotic agent.

Advantages over other “typical” antipsychotic agents, (e.g. haloperidol and droperidol), are said to include:

- Less incidence of acute dystonic reactions
- Less cardiac side effects

See also separate Document on Olanzapine Overdose (in Toxicology folder).

Chemistry

Olanzapine belongs to thienobenzodiazepine class of drugs.

Classification

There is no formal classification of the antipsychotic agents, however by tradition they are loosely divided into two principal groups.

1. The older “**first generation**” or “**typical**” group.
2. The newer “**second generation**” or “**atypical**” group.

In general the second generation agents have significantly less adverse effects profiles such as sedation, extrapyramidal side effects, anticholinergic effects or the development of neuroleptic malignant syndrome. The risk of these particular adverse effects although small is not completely eliminated with the second generation agents.

It has also been claimed that the second generation agents are more effective against the “negative” symptoms of schizophrenia, but this has *not* been convincingly proven as a *class* effect.

It should be noted that designating antipsychotics as first generation and second generation may be of limited value as it probably exaggerates the differences between groups and overstates similarities between members within each group. On this basis some prefer not to use this classification; nonetheless the terminology remains widely used.

First Generation Antipsychotic Agents :

These fall into two major groups:

1. **Phenothiazines:**
 - *Lower potency:*

- Chlorpromazine.
- Pericyazine.
- Thioridazine.
- *Higher potency:*
 - Fluphenazine.
 - Flupenthixol
 - Prochlorperazine
 - Trifluoperazine.
 - Zuclopenthixol

2. **Butyrophenones:**

- Droperidol.
- Haloperidol.

Second Generation Antipsychotic Agents :

These include:

1. Amisulpride
2. Aripiprazole
3. Asenapine
4. Clozapine
5. **Olanzapine**
6. Paliperidone
7. Quetiapine
8. Risperidone
9. Ziprasidone

Preparations

Tablets:

- 2.5 mg, 5.0 mg, 7.5 mg, 10 mgs

Wafers:

- 5mg, 10mg. these are dissolvable in water or in the mouth, and are rapidly acting.

Ampoules:

- 10 mg

Olanzapine pamoate:

- This is an IM depot **slow release** preparation: 210 mg or 300 mg vials.

Pharmacodynamics

Olanzapine is a selective monoaminergic **antagonist** at the following receptor sites:

1 Dopamine (D1-4)

- Antipsychotic actions are thought to be mediated (at least in part) by blockade of dopaminergic transmission in **D2** receptors in various parts of the brain (in particular the limbic system).³

Differential blockade of other dopamine receptors (eg D1) may influence therapeutic and adverse effects

Blockade of the following receptors also occurs and can result in adverse reactions, these receptors include:

2. Serotonin (5HT 2A/2C)
3. Muscarinic (M1-5) (anticholinergic effect)
4. Histamine (H1) (somnolence)
5. Adrenergic (α 1) (postural hypotension).

Pharmacokinetics

Absorption:

- Well absorbed either orally or sublingually, but there is a large first pass effect.

- IM administration results in rapid absorption with peak plasma concentrations occurring in 15 - 45 minutes.

Distribution:

- Vd is 10-20 L/kg
- Human placental transfer can occur.
- There is minor distribution only, into breast milk.

Metabolism and excretion:

- The half-life ranges between 21-54 hours (mean of 30 hours).
- Metabolized by the liver to inactive metabolites.

Indications

1. Agitation associated with an acute psychotic episode (such as schizophrenia)
2. Agitation associated with acute delirium
3. Bipolar disorder

Contraindications & Precautions

1. Olanzapine acts synergistically with other CNS depressants, particularly the benzodiazepines.
2. These effects are more pronounced when given by IM injection.
3. Hypotensive patients
4. Patients with prolonged QT syndromes
5. Aggravation of Parkinson's disease

Pregnancy

Olanzapine is categorized as a Class C drug with respect to pregnancy. Class C drugs are those which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialized texts should be consulted for further details. ¹

However ⁵....

Maternal use of olanzapine during pregnancy has **not** been associated with an increased risk of congenital malformations or adverse pregnancy outcomes.

However, (chronic) olanzapine use during pregnancy may result in increased infant birth weight and larger for gestational age infants.

Close monitoring is required throughout the pregnancy to prevent or manage metabolic complications such as excessive weight gain, increased serum triglyceride and cholesterol levels, glucose intolerance and/or gestational diabetes.

Olanzapine may also be associated with neonatal withdrawal syndromes, which include physical and behavioural symptoms such as irritability, restlessness, excessive crying, hypertonia, tachycardia and seizures.

Olanzapine should be used at the lowest effective dose in pregnant women if it is the medicine of choice .

There is limited information available regarding the long term effects of olanzapine on childhood development following exposure to olanzapine in utero.

Most studies have shown **no** significant differences on neurobehavioral development between exposed and non-exposed children.

Ultimately the decision to use olanzapine becomes a consideration of risk versus benefit.

On current knowledge one-off doses are unlikely to cause harm to the fetus. In the ED setting the benefits to a seriously disturbed and psychotic pregnant patient are very likely to outweigh any theoretical risk to the fetus.

Breast feeding:

Olanzapine is considered to be safe in breast feeding. ^{1, 5}

There is limited safety information available following the use of olanzapine during breastfeeding.

Very small amounts of olanzapine are excreted into breast milk but these amounts are unlikely to cause serious adverse effects in breastfed infants.

Observe the breastfed infant for adverse effects such as drowsiness, poor feeding and changes in sleeping patterns.

There is still a lack of information on developmental outcomes of infants exposed to olanzapine via breast milk.

Adverse Effects

These include:

1. CNS:

- Sedation
 - Lowering of seizure threshold, (though seizures are uncommon)
 - Extrapyrarnidal effects
2. CVS:
 - Hypotension, including orthostatic hypotension and tachycardia
 3. Neuroleptic Malignant Syndrome (NMS)
 4. Anticholinergic effects:
 - Tachycardia, blurred vision, mydriasis, constipation, nausea, dry mouth, urinary retention.
 5. Concurrent use of CNS depressants including alcohol

Dosing

Acute Behavioural Emergencies (Psychiatric Settings):

For the acutely disturbed younger patient with psychotic symptoms:

Oral:

- **Olanzapine 5 to 10 mg orally**, repeated every 2 to 4 hours, titrated to clinical response, up to a maximum of 30 mg in 24 hours, or 15 to 20 mg as a single initial loading dose on the first day. ¹

IM:

- **Olanzapine 5 to 10 mg IM**, repeated every 2 to 4 hours, titrated to clinical response, up to a maximum of 30 mg in 24 hours ¹

Acute Behavioural Emergencies (Emergency Medical Settings):

Acute medical settings are considered to be settings in which cardiorespiratory resuscitation resources are *immediately* available and staff are highly trained and experienced in their use.

The intravenous route is generally preferred for achieving **rapid** tranquilisation, if necessary to the point of sedation, because it allows titration of the dose and provides a more immediate effect.

If a patient cannot be physically restrained to the point where an intravenous line can be established without risk of harm to staff members, then initial intramuscular medication is appropriate.

In all cases, undertake post-medication monitoring and management.

When olanzapine is used in these types of settings:

- **Olanzapine 5 mg IV, repeated every 5 minutes, titrated to clinical response, up to a maximum of 20 mg.**
- **If adequate control is not achieved after 20 mg has been given, seek specialist advice.**

Olanzapine is not currently licensed for intravenous use, but research supports its use by this route. ⁴

The intramuscular formulation of olanzapine can be used for intravenous administration.

Intravenous olanzapine has the same onset of action as droperidol, but it is longer acting so there may be less need for re-sedation. ¹

Delirium in the Elderly:

In the elderly patient with acute delirium use:

- **Olanzapine 2.5 mg orally, as a single dose**
- **Olanzapine 2.5 mg IM, as a single dose.**

References:

1. eTG July 2016
 - Acute Behavioural Emergencies; Psychotropic Therapeutic Guidelines 7th ed 2013.
2. Olanzapine in L Murray et al. Toxicology Handbook 3rd ed 2015.
3. Australian Medicines Handbook, July 2013
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5. Olanzapine in RWH Pregnancy & Breastfeeding Guidelines, 25 July 2016.

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