THE NORTHERN HOSPITAL

MONOAMINE OXIDASE INHIBITORS

"Bistro", oil on panel, Jeremiah Stermer, 2001

"I saw my life branching out before me like the green fig tree in the story. From the tip of every branch, like a fat purple fig, a wonderful future beckoned and winked. One fig was a husband and a happy home and children, and another fig was a famous poet and another fig was a brilliant professor, and another fig was Ee Gee, the amazing editor, and another fig was Europe and Africa and South America, and another fig was Constantin and Socrates and Attila and a pack of other lovers with queer names and offbeat professions, and another fig was an Olympic lady crew champion, and beyond and above these figs were many more figs I couldn't quite make out. I saw myself sitting in the crotch of this fig tree, starving to death, just because I couldn't make up my mind which of the figs I would

choose. I wanted each and every one of them, but choosing one meant losing all the rest, and, as I sat there, unable to decide, the figs began to wrinkle and go black, and, one by one, they plopped to the ground at my feet.

...If neurotic is wanting two mutually exclusive things at one and the same time, then I'm neurotic as hell. I'll be flying back and forth between one mutually exclusive thing and another for the rest of my days".

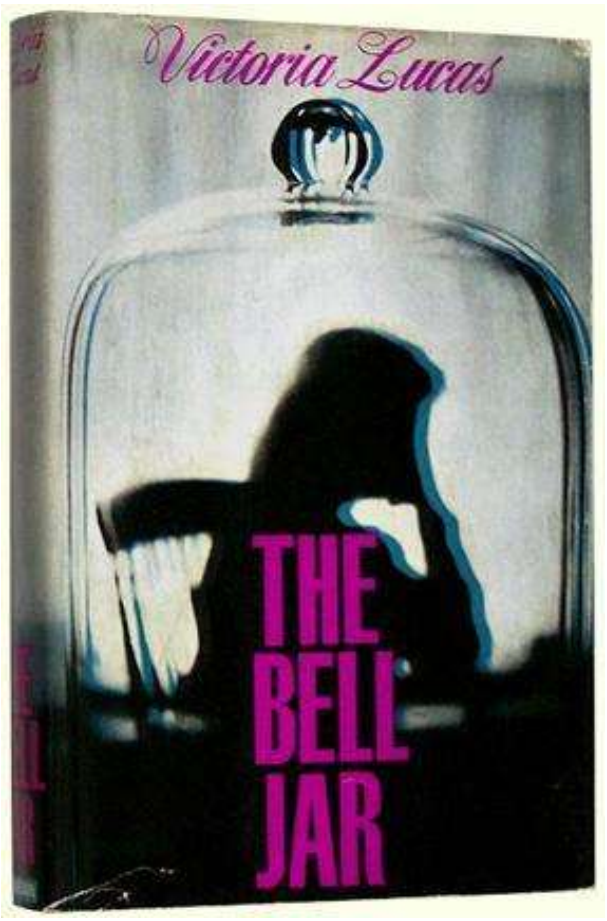
Sylvia Plath, "The Bell Jar", 1963.

Sylvia Plath was the first writer/ poet to posthumously win a Pulitzer Prize. One of her most famous works was "The Bell Jar" published in 1963, shortly before her suicide. It was extremely controversial at the time because of its intense autobiographical nature which described many aspects of, (in the insightful words of Dr Robyn Parker), her "slow burning depression" that would eventually lead to her suicide, by carbon monoxide poisoning at the tragically young age of just 30 years. It was feared "The Bell Jar" would have adverse influence over the psyche of the young. Although published under the pseudonym of "Victoria Lucas" in Britain in 1963, it would not be published in the United States until 1971.

Sylvia seems to have fitted the archetypal profile of the sufferer of "endogenous depression". From a young age she appeared to have it all, gifted writer, athletic, beautiful, and married to one of the times' most handsome and famous writers, the future British Poet Laureate, Ted Hughes. Yet even with all of this she appears to have been so depressed about her mundane "suburban" existence that mutually excluded all possibility of exciting romance, creativity, spontaneity or adventure that she felt she was living captive within an oppressive "bell jar", unable to escape.

The first antidepressant agents, the tricyclics and the monoamine oxidase inhibitors were discovered and introduced during the late 1950s; the first time in history an effective anti-depressant agent had become available to the medical profession. Silvia's doctor by the late 1950s had become so concerned about her state of mental health that he had decided to prescribe one of these new "wonder drugs". What was not initially appreciated in those early days of prescribing was the fact that a number of weeks were required for the full benefit of these medications to take effect. Sylvia Plath committed suicide just a few days after being commenced on her medication. It is possible to speculate that an earlier introduction of the medication may have saved her life.

In the hyper-realist painter, Jeremiah Stermer's arresting work, "Bistro", we perhaps get a feel for the "Bell Jar" of Sylvia Plath. The work has a disturbing dichotomy about it. On the one hand the setting is most intimate and idyllic, the softly lit restaurant and table for two - a couple that seem to "have it all". Yet the beautiful woman is not interacting with her unseen partner, she appears distant and distracted for what reason we can only guess at. It may be a lovers tiff, or it may be something unexplained or endogenous. Perhaps she is taking a MAO inhibitor in a desperate attempt to stave off her endogenous depression. She has not yet divulged her mental illness to her new lover and must now do this in order to explain her refusal of the magnificent glass of red wine put before her. She does not know if he will understand...others have not understood. She suddenly turns her face to hide a welling tear.



Left: Sylvia Plath, late 1950s. Right: First Edition of "The Bell Jar", published in 1963, under the pseudonym of "Victoria Lucas"

MONOAMINE OXIDASE INHIBITORS

Introduction

The older irreversible non-selective MAO inhibitors (MAOI) have significant and potentially lethal toxicity in overdose. A withdrawal syndrome is also recognized.

Isolated overdose with the newer reversible and selective agents have a benign course, unless there is co-ingestion of other serotonergic agents, in which case severe serotonergic syndrome may ensue.

In addition to the toxicity of acute overdose, MAOIs may also have significant adverse food reactions induced by **tyramine.**

Physiology

Neurotransmitters are generally monoamines, (noradrenaline, adrenaline, serotonin and dopamine)

When released into the synaptic space, neurotransmitters are either reabsorbed into the nerve cell and metabolized or metabolized in the synaptic cleft. COMT (catechol-O-methyl-transferase) is an extracellular enzyme. MAO is an intracellular enzyme, being found on the outer surface membranes of mitochondria.

MAO-A mainly metabolizes noradrenaline, adrenaline, serotonin and tyramines.

MAO-B mainly metabolizes dopamine.

It is hypothesized that clinical depression is related to a decreased concentration of the neurotransmitters.

For this reason, pharmaceutical research has produced drugs that can either block the reuptake of neurotransmitters (eg, cyclic antidepressants, newer selective serotonin reuptake inhibitors) or interfere with the breakdown of the monoamines within the synaptic cleft (monoamine oxidase inhibitors or "MAOIs").

MAOI Classification

Non Selective Agents (ie inhibit both MAO-A and MAO-B):

Irreversible agents:

Hydrazines:

- Phenelzine
- Isocarboxazid

Non-hydrazines:

- Tranylcypromine

Selective Agents: (ie inhibit either MAO-A or MAO-B):

Irreversible agents:

MAO-B inhibitors:

- Selegiline (used in Parkinsons disease)

Reversible Agents:

RIMAs, (i.e. short acting **r**eversible **i**nhibitors of **M**AO-**A**)

- Moclobemide

Toxicology

With respect to the toxicity of these agents:

The **older irreversible non-selective** monoamine oxidase (MAO) inhibitors are associated with:

- Serotonin toxicity in acute overdose which can be lethal.
- Sympathomimetic toxidromes.
- A withdrawal type syndrome.

The **newer reversible and selective** MAO inhibitors are associated with:

- A generally benign coarse in acute and isolated overdose.
- Severe serotonin syndrome when taken in combination with other serotonergic agents.

In more general terms, all may cause:

- A sympathomimetic toxidrome, which may also be initiated by adverse drug and food (**tyramine**) reactions.

Irreversible non-selective blockade of MAO-A and MAO-B will require new enzyme synthesis over days to re-establish proper function.

In overdose these agents will result in elevated levels of serotonin, adrenaline, noradrenaline, dopamine and phenylmethylamine. The resulting sympathomimetic toxidrome may then persist for days.

MAOIs in combination with other serotonergic agents or tyramine rich foods may result in serotonin toxicity.

Potential drug interactions:

- Pethidine
- Dextromethorphan
- Selective serotonin reuptake inhibitors (SSRIs) - fluoxetine, paroxetine
- Sertraline
- Sumatriptan
- All serotonergic agents in general may lead to the "serotonin syndrome", (see separate guidelines)

Tyramine containing foods:

- Aged cheeses
- Red wine (much more so than white wine).
- Beer
- Aged, pickled, or smoked meats (eg, salami)
- Yeast extracts
- Avocado
- Sauerkraut

Pharmacokinetics

Absorption

- All MAOIs are well absorbed orally and reach peak levels within 2-3 hours.
- There is generally extensive first pass metabolism

Distribution

- They generally have moderate volumes of distribution, (eg: moclobemide is 1.2 L/kg)

Metabolism and excretion

- They undergo hepatic metabolism
- Some such as phenelzine, tranylcypromine and selegiline, have active metabolites.

Risk Assessment

The non-selective irreversible agents may result in severe and lethal serotonin and sympathomimetic toxicity.

Symptoms can be delayed in onset and may persist for days.

The newer selective and reversible agents tend to run a more benign course when taken in isolation. Severe serotonin syndrome may result however when taken in combination with other serotonergic agents.

Specific dose related risk assessments:

Moclobemide:

- This causes minor symptoms only, even with large doses.
- Significant serotonin syndrome may occur however if there is co-ingestion with another serotonergic agent.

Phenelzine:

- > 2 mg/kg is associated with toxicity.
- > 4-6 mg/kg is potentially fatal.

Tranylcypromine:

- > 1mg/kg is associated with toxicity.
- 170 mg has resulted in documented fatality.

Clinical Features

Symptomatology of intentional overdose may be delayed for 6-12 hours post ingestion

These patients require prolonged close monitoring to prevent morbidity.

MAOI overdoses or interactions present with excessive catecholamine stimulation toxidromes.

Late in the course, the patient may become hypotensive and comatose.

Symptoms can be classified into mild, moderate, and severe.

Features of acute overdose may include:

Mild symptoms:

- Agitation, (in contrast to TCAs which cause sedation)

- Confusion
- Flushing
- Diaphoresis

Moderate symptoms:

- Altered mental status
- Mild pyrexia
- Hypertension
- Tachycardia
- Tachypnea

Severe symptoms:

- Severe hyperpyrexia, (> 39.5^0 C)
- CNS: coma and seizures
- Respiratory depression
- Muscle rigidity
- CVS, serious arrhythmias are not usually a feature of MAOI overdose.
    - ♥ Moderate hypertension may occur initially, however, severe hypotension may follow, (peripherally acting MAOIs may allow the accumulation of many different amines, which act as false neuro-transmitters)
    - ♥ Note that true hypertensive crises is not usually seen in the setting of acute overdose. It is usually seen in association with drug or tyramine containing food interactions.

Investigations

Blood tests

- FBE
- U&Es/glucose
- CK (rhabdomyolysis)
- Troponin level
- Consider co-ingestion, paracetamol and blood alcohol levels

ECG

- Look for arrhythmias.
- Specifically with **moclobemide:**
  - ♥ Mild prolongation of the QT may occur.
  - ♥ There should be a 12 lead ECG at presentation and again at 6 hours.
  - ♥ If the QT is > 500 ms, then ongoing monitoring is indicated.

Drug screening

- Quantitative levels of MAOIs are not routinely done and are not clinically useful.

Other tests are done as clinically indicated.

Management

1. Attention to any immediate ABC issues.
2. Activated charcoal:
   - This may be used if the patient presents within two hours and there are **no symptoms**, and if > 1mg/kg of tranylcypromine, or > 2mg/kg of phenelzine has been ingested.
   - Charcoal is contra-indicated in any symptomatic patient because of the likelihood of further deterioration.
3. Fluids:
   - IV fluid hydration is important.
4. Agitation:
   - Treat agitation with IV diazepam.
5. Seizures:
   - Control seizures along conventional lines
6. Hyperthermia:
   - Any hyperthermia will require aggressive treatment, (IV fluids and benzodiazepine sedation, external cooling)
   - Severe hypertension (> 39.5^0 C), intubation, paralysis and ventilation to prevent multiple-organ failure and permanent neurological injury.

- Look for and treat any associated rhabdomyolysis.

7. Hypertension:

   - Titrated IV benzodiazepines may be sufficient to control hypertension.

   - GTN or nitroprusside infusions may be used to treat severe hypertension, (**avoid** beta blockers as these will leave unopposed alpha effects that may worsen hypertension)

   - Alternatively, IV 2-3 mg phentolamine, every 10-15 minutes until blood pressure is controlled.

8. Serotonin syndrome:

   - Life-threatening serotonin syndrome will require intubation, paralysis and ventilation.

   See separate Serotonin toxicity guidelines

Disposition:

Because symptoms of intentional overdose may be delayed for 6-12 hours post ingestion all patients should be admitted for observation for a **minimum of 12 hours.**

"Still Life with Cheeses", oil on wood, Floris Claesz van Dijck, 1615, Rijksmuseum Amsterdam.

Cheeses as well as red wine are also high in tyramine, and are best avoided in those taking MAOIs.

References

1. MAOI overdose in L Murray et al. Toxicology Handbook 2nd ed 2011.

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