

IMIPRAMINE



Portrait of Simonetta Vespucci, tempera on wood, early Renaissance. 1490, Piero di Cosimo. Musée Condé, Château de Chantilly

....I was returning through the deserted streets of the metropolis by the last omnibus "outside" as usual on the top deck. I sank into a daydream, and lo the atoms danced before my eyes. Whenever hitherto, these diminutive beings had appeared to me, they had always been in motion, but up to that time I had never been able to discern the nature of their motion. Now, however, I saw how frequently two smaller atoms united to form a pair; how a larger one embraced two smaller ones; how still larger ones kept hold of three or even four of the smaller; whilst the whole kept whirling in a giddy dance. I saw how the larger ones formed a chain, dragging the smaller ones after them, but only at the ends of the chain....The cry of the conductor "Clapham Road" roused me from my daydream, but I spend part of the night putting at least sketches of these musings down on paper. This is how the structure theory first came into being.

.....I was sitting writing at my textbook; but I was not progressing, and my mind began to wander. I turned my chair to the fire and began to doze. Again the atoms began to dance before my eyes. This time the smaller groups kept modestly in the background. My mind rendered more acute by repeated visions of the kind, could now distinguish larger structures of manifold conformation: long rows sometimes more closely fitted together, all twining and twisting in snake-like motions. But look! What was that? One of the snakes had seized hold of its own tail, and the form whirled mockingly before my eyes. As if by a flash of lightening I awoke; and this time I also spent the rest of the night in working out the consequences of my hypothesis....

*August Kekule,
Address to the German Chemical Society, 1890,
on his discovery of the structure of the
benzene molecule in 1858.*

By the mid-Nineteenth century, Chemistry, as a discipline of scientific study, had been well established for over a century, having superseded the mysticism of alchemy of earlier times. One of the holy grails of chemistry at this time was the determination of the precise atomic structure of molecules. Relative proportions of various elements that made up various molecules were by now well known, but just precisely how the elements were arranged within many molecules remained a profound mystery. What was known for sure, was that in order to make the next advances in chemistry a deeper understanding had to be obtained about how elements came together to form molecules.

The compounds that were being studied in this great endeavour were known collectively as the "aromatics" because of their pleasant smell or "aroma". It was known that these compounds were somehow related to benzene, and so to understand more complex molecular structures, it was essential to first understand the benzene molecule. It had been established that atoms of elements seemed to have certain "valances", which described the ability of an atom to form a bond with another atom. Hydrogen for example had a valance of one and so could form one bond with another atom, while oxygen had a valance of two and so could form two bonds with other atoms. In this way the classic atomic structure of water was determined as H_2O , that is one oxygen atom combined with two hydrogen atoms to form one molecule of water.

Carbon had a valence of four and so it was easy to understand the structure of a molecule like methane as being CH_4 . But there were many molecules whose elemental proportions did not seem to make any sense, given their valences. Benzene for example had a very unusual chemical formula, C_6H_6 and so its molecular structure remained a total mystery. The Scottish chemist, Archibald Scott had made some progress when he recognized that carbon atoms sometimes behave as if they have a valence of two instead of four. This could occur, he realized, if a double bond (rather than simply a single one) linked carbon to other atoms. By this reasoning the molecular structure of carbon dioxide was determined, its known proportions of two oxygen atoms for each carbon atom could be imagined as $\text{O} = \text{C} = \text{O}$ or CO_2 .

This insight caught the attention of a brilliant German chemist by the name of Friedrich August Kekule. At first he was somewhat sceptical of Scott's theory, but he kept an open mind, and the idea would play a crucial role in his work that followed. Kekule had been labouring for many months with the problem of the structure of benzene. It became such an obsession to him that benzene occupied not only his every waking thought, but also his subconscious thought. He famously described how even when riding on an omnibus, little molecules of carbon "danced" before his mind in daydreams. Then late one evening when he could no longer work anymore through sheer mental exhaustion he decided to take a rest. He turned his chair towards his fireplace, and while watching the flames he dozed off. In a twilight state between consciousness and sleep he again imagined carbon atoms dancing before his eyes. They began to form long undulating chains, dragging other atoms along with them. Some of them began "twining and twisting" in snake-like motions. Suddenly one of these grabbed hold of its own tail. "But look!" he later recorded of his vision, "What was that? One of the snakes had seized hold of its own tail, and the form whirled mockingly before my eyes!" Then "As if by a flash of lightning I awoke!" With a palpitating heart, he worked furiously into the night and early hours of the morning working out the possibilities and consequences of carbon atoms linking together not in chains, but in rings with alternating double bonds.

History is replete with stories of miraculous flashes of novel insight by brilliant people that would change the course of human history. Often times these insights came in an idle observation of a mundane everyday event, like Archimedes taking a bath or Werner Heisenberg watching a figure in the night appearing in lamp light one minute then becoming invisible then next minute in darkness as it moved from lamp to lamp. But fascinatingly many other insights have come from dreams. Dmitri Mendeleev formulated the Periodic Table after a vision in a dream. Julia Ward Howe, wrote out "Mine Eyes Have Seen the Glory", (Battle Hymn of the Republic) in the middle of the night, after awaking from a spectacular dream she had had.

As August Kekule dozed in front of the crackling flames his subconscious mind began to play tricks. Now unfettered by the external world, myriad images from his vast learning and life's experiences arose from his subconscious and merged with his dancing atoms. Suddenly one undulating carbon snake metamorphosed into an ancient symbol for eternity known as the Ouroboros, a snake that bites its own tail forming a ring. He awoke with a start, as if struck by lightning. The benzene molecule was a ring! It was a eureka moment, a conceptual quantum leap. Much of the chemistry of life is based on cyclic

molecular structures - and benzene was “the one ring to rule them all”. It was the birth of Organic chemistry.

Kekule, like all highly educated people of his time, was well versed in classical history, and the Ouroboros symbol of the snake biting its own tail would have been well known to him. The origins of the Ouroboros are obscure, but are certainly very ancient. The earliest known appearance of the motif is in the Enigmatic Book of the Netherworld, a 14th century BC Egyptian funerary text discovered in the tomb of Tutankhamun. The symbol entered the Western cultural tradition during the Greek Classical Age. Later it was incorporated into Western Medieval alchemy.

By the early Renaissance the Ouroboros had become a strong and recurring Artistic motif, symbolizing the cycles of life, eternity, as well as the indivisible self-sustaining powers of nature. We see for example the image of the Ouroboros in Piero di Cosimo's enigmatic “Portrait of Simonetta Vespucci”, tempera on wood, 1490. Simonetta was born Simonetta Cattaneo circa 1453, in the Republic of Genoa. By the age of sixteen she was said to be the most beautiful woman in all of Italy. Legend has it that she was the model for Sandro Botticelli's Venus, in the “Birth of Venus”, one of the most beautiful works of the early Renaissance. In 1469 she was married to Marco Vespucci, son of Piero Vespucci who was related to the famous explorer and cartographer Amerigo Vespucci, after whom the American continents are named. Marco's family had connections to the powerful Medici family in Florence where the couple went to live. Simonetta was a sensation in Florence, the Medici in particular were entranced. In 1475, a tournament was held in the Piazza Santa Croce, where Giuliano Medici competed bearing a banner upon which appeared Simonetta's portrait as a helmeted Pallas Athena, painted by Botticelli. Beneath her portrait was an inscription in French, “La Sans Pareille”, “The Unparalleled One”.

But then tragedy. Simonetta Vespucci died just one year after the tournament, probably from that most ubiquitous killer of young people in those times, an infectious disease; in Simonetta's case this was possibly tuberculosis. She was twenty two years old. All of Florence was devastated. She was carried through the city in an open coffin for all to pay their respects. It was said that for a time afterwards a posthumous cult developed in Florence dedicated to her memory. In Piero di Cosimo's portrait we see Simonetta wearing a golden necklace, symbol of worldly riches, but coiled about this is a snake, about to latch onto its own tail; it is the Ouroboros the symbol of the cycle of life and of death.

August Kekule's image of the Ouroboros that came to him in a dream unlocked the key to organic chemistry. From this point in 1858, progress became ever more rapid, until in just under a century later in 1953, two brilliant molecular biologists, Englishman, Francis Crick and American, James Watson, determined the structure of the molecules of all life on Earth, deoxyribonucleic acid (DNA) and ribonucleic acid, (RNA). Both molecules are built around aromatic ring structures.

Before the middle of the Twentieth century, there were no effective pharmacological treatments for major depression. But in 1950s the first were developed, the monoamine oxidase inhibitors and tricyclic antidepressants. Imipramine was the prototype tricyclic

antidepressant. Its molecular structure, like all the TCAs was based on a triple benzene ring core. Though the Ouroboros symbolized the end of life for Simonetta Vespucci, for many severely depressed of the mid-Twentieth century it symbolized the hope of a renewed life.



Top: The earliest known representation of the Ouroboros - tomb of Tutankhamen, 14th century BC.



Left: Stylized Ouroboros from the Book of Kells, 9th century AD.

IMIPRAMINE

Introduction

Imipramine (trade name in Australia “Tofranil”) is an old **tricyclic antidepressant (TCA)** agent.

It was the prototype of its class.

TCAs inhibit the reuptake of **noradrenaline** and **serotonin** into presynaptic terminals.

Imipramine, like all TCAs has significant toxicity in overdose and is high risk for lethality

It is for this reason that imipramine is now rarely used to treat depression, especially in view of the fact that newer and much safer agents, such as the SSRIs are available.

It should be avoided in patients with a history of overdose or of high risk for overdose. Safer agents should be used.

It retains some minimal clinical use in situations where patients do not respond to, or are intolerant of, other agents.

It is best prescribed under the supervision of a Psychiatrist.

See also separate document on Tricyclic Antidepressant Overdose (in Toxicology folder).

History

Imipramine was developed in 1951 and was introduced into clinical practice in the US in 1957.

Imipramine was the prototype TCA and it was the first TCA to be developed for clinical use.

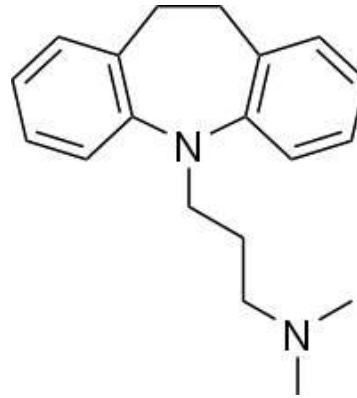
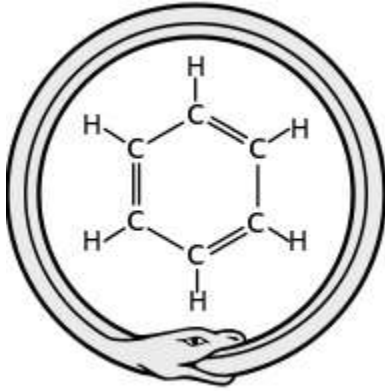
It has been superseded by safer agents such as the **SSRIs**.

Chemistry

The classical prototypical structure of the tricyclic antidepressants is the **triple benzene-ring**.

Benzene is an organic molecule with the chemical formula C_6H_6 . It is composed of 6 carbon atoms joined in a ring with one hydrogen atom attached to each.

As it contains only carbon and hydrogen atoms, benzene is classed as a hydrocarbon. Due to its ring structure is classed as an aromatic hydrocarbon .



Left: The Ouroboros, Freidrich August Kekule's inspiration for the molecular structure of benzene.

Right: The core triple "aromatic" ring structure of all TCAs.

Classification

Antidepressants can be loosely classified into 6 groups:

1. **Tricyclic antidepressants (TCAs):**

TCAs inhibit the reuptake of **noradrenaline** and **serotonin** into presynaptic terminals.

Examples include:

- Amitriptyline
- Clomipramine
- Dothiepin
- Doxepin
- **Imipramine**
- Nortriptyline
- Trimipramine

2. **Monoamine oxidase inhibitors (MAOIs):**

These agents block of MAO-A and/ or MAO-B, thereby increasing the synaptic concentrations of **adrenaline, noradrenaline, dopamine** and **serotonin**.

Examples include:

- Phenelzine
- Tranylcypromine

3. **Selective serotonin reuptake inhibitors (SSRIs):**

The SSRIs selectively inhibit the presynaptic reuptake of **serotonin**

Examples include:

- Citalopram
- Dapoxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline

4. **Serotonin- norepinephrine reuptake inhibitors (SNRIs):**

These are **serotonin and noradrenaline** reuptake inhibitor.

Examples include:

- Venlafaxine
- Desvenlafaxine
- Duloxetine

5. **Tetracyclic antidepressants:**

These have a tetracyclic chemical structure, containing four rings of atoms.

They are closely related to the tricyclic antidepressants (TCAs), which contain three rings of atoms.

Examples include:

- Mianserin
- Mirtazapine

6. **Atypical Antidepressants:**

Essentially other newer agents not belonging to the above groups

Broadly described as atypical antidepressants, they affect serotonin, norepinephrine, and dopamine levels in varied and unique ways.

Preparations

Imipramine hydrochloride as:

Tablets:

- 10 mg
- 25 mg

Mechanism of Action

TCAs inhibit reuptake of **noradrenaline** and **serotonin** into presynaptic terminals.

Unrelated to the therapeutic effects of the TCAs, they also **block** the following receptors:

- Cholinergic
- Histaminergic
- Alpha1-adrenergic
- Serotonergic receptors.

Clomipramine has a greater effect on serotonin transport than other TCAs.

Pharmacodynamics

The therapeutic activity of imipramine is believed to be based mainly on its ability to inhibit the neuronal re-uptake of noradrenaline norepinephrine and serotonin (5-HT).

Although adverse effects may appear early, therapeutic response can take up to 2 weeks.

Pharmacokinetics

Absorption:

- Imipramine is administered orally.
- Oral bioavailability is around 94 - 96%.

Distribution

- The mean volume of distribution is 21 L/kg.
- Protein binding is around 89%.
- Imipramine can cross the human placenta.
- Imipramine and its metabolite desipramine are distributed into human breast milk in small amounts.

Metabolism and excretion:

- Imipramine is metabolized in the liver to a range of metabolites.
One metabolite desmethyl-imipramine, also exhibits antidepressant activity.
- The mean plasma half-life is approximately 20 hours.

Indications

1. Major depression:
 - However its place has now largely been taken by newer less toxic agents, such as the SSRIs.
It may be considered by Psychiatrists in situations where other agents are contraindicated or not tolerated.
2. Panic disorder (as a second line agent).

Contra-indications/precautions

Contra-indications/precautions for the TCAs as a class include:

1. Known hypersensitivity.
2. Monoamine oxidase inhibitors (MAOIs).

- TCAs should not be given *concurrently* with monoamine oxidase inhibitors including selegiline.

The combination of TCAs with a monoamine oxidase inhibitor may cause severe hyperpyretic reactions and death.

When it is desired to substitute a TCA for a monoamine oxidase inhibitor, a **minimum of 14 days** should be allowed to elapse after the latter is discontinued.

TCAs should then be initiated cautiously with gradual increase in dosage until optimum response is achieved.

3. Patients at high risk for overdose:

- **All TCAs have significant toxicity in overdose and are high risk for lethality**

It is for this reason that TCAs are now rarely used to treat depression, especially in view of the fact that newer and much safer agents, such as the SSRIs are available.

They should be avoided in patients with a history of overdose or of high risk for overdose.

Use safer agents.

4. Proarrhythmic effects:

- Use with caution in patients with cardiac disease.

5. Seizures:

- TCAs should be used with caution in patients with a history of seizures

TCAs, in general and especially clomipramine, may increase the risk of seizures.

Risk is dose-dependent and is greatest at the start of treatment and when there is a dose increase.

Use TCAs with caution, with low doses and slow titration.

6. Caution in patients in whom anticholinergic effects would be problematic

For example:

- Chronic constipation
 - Prostatism
 - Glaucoma
7. Hepatic impairment:
- Halve the dose in severe impairment.
- Consider using a TCA for which serum concentrations can be measured, e.g. nortriptyline.
8. Children
- TCAs are not recommended for treating depression in children as they are not effective
9. Elderly:
- **Nortriptyline** is often chosen as the TCA of preference for elderly people because it is less likely to cause hypotension, sedation and anticholinergic effects.
- Serum drug concentration can be also used to guide dosage.

Pregnancy

Imipramine is classed as a category C drug with respect to pregnancy.

Category C drug are those drugs 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.

There is limited safety information available following the use of imipramine during pregnancy.

Most studies have shown that there is no significant increased risk of congenital malformations with maternal use of tricyclic antidepressants.

However, newborns exposed to imipramine, especially in late pregnancy may experience neonatal withdrawal symptoms. This 1 to 2 week period of self-limiting neonatal antidepressant withdrawal symptoms may present within the first 24 hours or up to several days after birth and may require supportive treatment.

Inform neonatal care providers about the use of imipramine as adverse effects or withdrawal symptoms may present in the newborn.

Based on the limited information available, long term neurobehavioral and cognitive outcomes among children exposed to TCA in utero have shown no significant difference compared to non-exposed children.

Breast feeding

Small amounts of imipramine and the metabolite desipramine are excreted into breast milk, but no serious harmful effects have been noted in breastfed infants.

If imipramine is the medicine of choice, use the lowest effective dose, preferably as a single bed time dose and observe the infant for adverse effects such as excessive drowsiness, irritability, poor feeding and restlessness. Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant.

A small study has shown that there was no significant difference between the mental and psychomotor development of breastfed infants exposed to imipramine compared to bottle-fed infants.

Adverse Effects

Adverse effects of the TCAs as a class include:

1. CNS:
 - **Sedation**
 - Agitation / anxiety
 - Insomnia
 - Confusion
 - Seizures (rarely).
2. CVS:
 - Orthostatic hypotension
 - Sinus tachycardia
 - Tachyarrhythmias
 - TCAs may prolong the QT interval
3. Anticholinergic effects

These may result in the classic anticholinergic effects:

- Blurred vision (paralysis of accommodation) / mydriasis.
- Dry mouth
- Urinary retention
- Constipation
- Glaucoma:
 - ♥ Due to anticholinergic effects, TCAs should be used with caution in patients with narrow angle glaucoma or increased intraocular pressure.

In patients with narrow angle glaucoma, even average doses precipitate an attack.

4. Psychiatric:

- Increased suicidal thoughts
 - ♥ Increased suicidal thoughts and behaviour can occur soon after starting antidepressants in general, particularly in young people.

Monitor patients frequently and carefully early in treatment
- All antidepressants may provoke a manic episode when used in people with bipolar disorder.

5. Hyponatraemia:

- As part of SIADH

Dosing

Depression:

Usual adult dosing is:

- Oral 25 - 75 mg daily,
Increasing by 25 - 50 mg every 2 - 3 days to 75 - 150 mg daily.
Maximum dosing is **300 mg daily**.

It may be given as divided doses or as a single dose at night.

Panic disorder:

For panic disorder start with a low dose and slowly increase to minimise adverse effects (e.g. increased anxiety, agitation) usually up to 150 mg daily although higher doses may be needed.



Left: Engraving of an ouroboros in a 1625 alchemical tract “De Lapide Philosophico” by Lucas Jennis. Here the dragon image serves as a symbol for the element mercury.



Right: John William Waterhouse’s “The Magic Circle”, oil on canvas, 1886 - the sorceress wears a snake around her neck as an Ouroboros. As she casts a spell, she traces out the ouroboros in the sand.





August Kekule (1829 - 1896)

References

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