

DULOXETINE



*“Sunflower Seeds”, handmade and hand-painted porcelain (approximately 8 million);
Installation, Ai Weiwei, Tate Gallery, London, 2010.*

“Ideas alone can be works of art; they are in a chain of development that may eventually find some form. All ideas need not be made physical....All of the significant art of today stems from Conceptual art. This includes the art of installation, political, feminist, and socially directed art”

Sol LeWitt, “Paragraphs on Conceptual Art”, 1967.

In the late 1960s and early 1970s an avant-garde genre of Art began to emerge that emphasized ideas or concepts over traditional materials, methods and skills that were

usually used in the production of works of Art. This genre was very confronting for its times, challenging the very notion of what Art was or what it could be. The term "Conceptual art" came to be used as an umbrella designation that described the explosive radiation of the new "idea" art. The "Conceptualists" looked beyond the constraints of traditional Art media, and began to produce provocative works, often termed "installations"; that conveyed subliminal messages about society, culture, and politics. It was a socially directed Art form where the idea was more important than the final concrete result. Conceptualism was influenced by minimalism and even the bizarre Dada movement of the 1920s. Despite heated and vitriolic attack from established circles, Conceptual Art did catch the imagination and interest of the wider public, and it became extremely influential and has remained so to the present day.

Perhaps the most famous "Conceptualist" today is Chinese Artist Ai Weiwei. His works are strongly influenced by the Pop Art of the 1960s, Andy Warhol in particular. Indeed the National gallery of Victoria hosted a combined Warhol-Ai Weiwei exhibition in 2016. Although influenced by Warhol, Ai Weiwei's work is by no means simply "Pop Art". Warhol's work was more social commentary, whereas that of Ai Weiwei is far more a political commentary. It is also far more "Conceptual" in its presentation. One of his most famous installations was "Sunflowers" at the Tate Modern. This work consisted of a vast carpet of millions of sunflower seeds made out of porcelain. The seeds were not mass produced from some factory. Although superficially alike each seed was individually handmade, sculptured and painted by skilled artisans in the city of Jingdezhen, famed for its production of Imperial porcelain. Each seed is incredibly realistic and each is unique. In the Tate installation, there are an astounding 8 million of them! Together they form one of the largest works in porcelain ever made. Over the course of two years, over 100 million of these were made, forming a mass of objects that weighs over 150 metric tonnes, and covers 1000 square metres. Originally patrons were invited to walk bare foot over the seeds or to lie down among them. Porcelain making is an old and quintessentially Chinese art form. Ai Weiwei's "Sunflower Seeds" invites viewers to contemplate interrelated social, economic, political and cultural issues.

The work seems to imply something about the mass scale and economic might of the "made in China" brand, but it has deeper cultural and personal connotations for Ai Weiwei himself. He grew up with his family in the repressive regime of communist China during the time of the "Cultural Revolution", of 1966-76.

He is asking his viewer difficult questions. "What does it mean to be an individual in today's society? – in China in particular! Where will our increasing desires for mass materialism lead us to into the future? Ai Weiwei himself has said "From a very young age I started to sense that an individual has to set an example in society. Your own acts and behaviour tell the world who you are and at the same time what kind of society you think it should be." During the Cultural Revolution individuals in China were stripped of all personal freedoms, and propaganda images depicted Chairman Mao as the sun and the masses of people as sunflowers all uniformly turned towards him!

But Ai remembers sunflowers and sunflower seeds from his childhood very much differently to the "official party line". For him the sharing of sunflower seeds among families was a deeply personal experience of goodwill, friendship, kindness and

compassion during a time of extreme hardship, poverty and brutal repression. The interaction of the viewers walking among the seeds, especially of young children delighting in playing among them, recreates nostalgic feelings of the sort felt by Ai Weiwei for his own childhood.

The frantic modern age with its treadmill lifestyle, has created unprecedented levels of stress related illnesses including anxiety and depression. Modern psychiatric theories hold that depression is simply a case of “chemical imbalance” in the brain. Not enough serotonin or noradrenaline is the cause. Big Pharma enthusiastically responds with the perfect antidepressants - elevate your brain serotonin and all will be well. The antidepressants are cosmically profitable – they do not cure but “manage” and so they treat a chronic condition that virtually everybody has at least at some stage of their lives. Antidepressants are mass produced on a scale that rivals the production of Ai Weiwei’s sunflower seeds, every year! Big Pharma would have us turn our faces like so many sunflowers towards the latest patent products such as duloxetine. But perhaps a more efficacious treatment of depression lies simply in the occasional escape from the frantic treadmill of modern day living whenever possible – refuge in the great works of art both past and present is not a bad start – the vision of sunflowers past by Vincent van Gogh or the vision of sunflowers seeds present by Ai Weiwei.



*Porcelain Sunflower Seed,
Ai Weiwei, 2010*

*“Still Life with 15 Sunflowers”,
oil on canvas, Vincent van Gogh,
1888.*

DULOXETINE

Introduction

Duloxetine (trade name “**Cymbalta**”) is a potent selective **serotonin *and* noradrenaline** reuptake inhibitor (**SNRI**).

The SNRIs are a relatively new class of antidepressant agents.

As a class the SNRIs are far more toxic in overdose than is the case with the SSRIs

See also separate document on:

- **Serotonin Syndrome (in Toxicology folder)**

History

Duloxetine was developed by Eli Lilly.

It was approved by the FDA for clinical use in 2004.

Cymbalta generated sales of nearly 5 billion USD in 2012 with 4 billion of that generated in the U.S

History

Duloxetine is chemically unrelated to tricyclics, alpha-adrenergic receptor agonists or antimuscarinics

Classification

The selective **serotonin reuptake inhibitors (SSRIs)** currently include:

1. Fluoxetine
2. Citalopram
3. Escitalopram
4. Fluvoxamine
5. Paroxetine
6. Sertraline
7. Dapoxetine

The **serotonin *and* noradrenaline reuptake inhibitors (SNRIs)** currently include:

1. Venlafaxine
2. Desvenlafaxine
3. **Duloxetine**

Preparations

Duloxetine hydrochloride as:

Capsules (enteric coated):

- 30 mg, 60 mg.

Mechanism of Action

Duloxetine a potent selective **serotonin and noradrenaline** reuptake inhibitor.

Duloxetine more potently inhibits the reuptake of serotonin compared to noradrenaline.

The antidepressant action of duloxetine in humans is believed to be associated with its potentiation of neurotransmitter activity within the central nervous system.

It weakly inhibits dopamine uptake.

It has no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

Pharmacokinetics

Absorption:

- Duloxetine is administered orally and is well absorbed.

Distribution:

- Duloxetine is highly (> 90%) protein bound to plasma proteins

Metabolism and excretion:

- Duloxetine undergoes extensive metabolism.

The 2 major metabolites found in plasma and urine are the glucuronide conjugate of 4-hydroxy duloxetine, and the sulfate conjugate of 5-hydroxy, 6-methoxy duloxetine.

The major circulating metabolites of duloxetine do not have significant pharmacologic activity

Pharmacodynamics

Duloxetine may be more effective than the SSRIs, and is least as effective as tricyclic antidepressants, in the treatment of major depression.

It should be noted however, that the SNRIs are far more **toxic in overdose** than is the case with the SSRIs.

Indications

Indications include:

1. Major depression
2. Generalized anxiety disorder
3. Painful diabetic peripheral neuropathy
 - Though not a first-line treatment; and appears less effective than the TCAs
4. Fibromyalgia
5. Chronic pain syndromes in general

Contraindications/ Precautions

As a class SNRI contraindications and precautions include:

1. Hypersensitivity to duloxetine.
2. CVS disease:
 - Caution in patients with hypertension / CVS disease
3. Caution with other **serotonergic** agents:
 - Coadministration with other serotonergic drugs (e.g. SNRIs, SSRIs, tramadol or triptans such as Sumatriptan, or MAOIs - selective, reversible or irreversible - within a minimum of 14 days) may result in **serotonin syndrome**.
4. Bipolar disorder: ²
 - All antidepressants may provoke a manic episode when used in people with **bipolar disorder**.

Some patients *without* a history of bipolar disorder may develop an antidepressant-induced manic episode; this does not necessarily imply a diagnosis of bipolar affective disorder.

5. Hepatic impairment:

- Dose should be decreased in hepatic impairment:
- **Duloxetine** is contraindicated in hepatic impairment. ²

6. Renal:

- Reduce dose if Cr Cl < 30 mL/minute and in haemodialysis patients.

7. Epilepsy:

- Epilepsy/ history of seizures
 - ♥ SNRIs may increase the risk of seizures (risk less than with TCAs).

Risk is dose-dependent and is greatest at the start of treatment and when there is a dose increase; use low doses and titrate slowly
- Other risks for reduced seizure threshold, including treatment with drugs that may increase the risk of seizures.

8. Bleeding: ²

- SNRIs, (like the SSRIs) may increase the risk of bleeding, especially gastrointestinal bleeding, by blocking the uptake of serotonin into platelets.

However, the absolute risk of this is **low**

Use with caution if the patient is at high risk of bleeding (e.g. age >80 years or previous upper GI bleeding) or taking drugs known to increase risk of GI bleeding (regular aspirin or NSAIDs).

Pregnancy ^{1,4}

Duloxetine is a category B3 drug with respect to pregnancy.

Category B3 drug drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

From the limited information available, maternal use of duloxetine has not been associated with an increased risk of congenital malformation.

Consultation with a perinatal psychiatrist is recommended if the initiation or continuation of duloxetine therapy is required during pregnancy.

Newborns exposed to duloxetine in utero, especially during late pregnancy, may experience self-limiting neonatal withdrawal symptoms.

These symptoms include respiratory distress, irritability, sleep disturbances, tremors, jitteriness and feeding difficulties. Inform neonatal care providers about the maternal use of duloxetine as supportive care may be required.

There is a lack of information on the long term behavioural and cognitive outcomes among infants exposed to duloxetine in utero.

Breastfeeding ^{1,4}

Considered to be safe.

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

Small amounts of duloxetine are excreted into breast milk, but the amount is very unlikely to cause serious harmful effects in the breastfed infant.

The actual amount of medicine absorbed by the infant is likely to be very small, as duloxetine is unstable under the acidic conditions in the infants stomach.

If duloxetine is the medicine of choice, use the lowest effective daily dose and closely observe the breastfed infant for adverse effects such as lethargy, jitteriness, poor feeding and agitation.

There is still a lack of information regarding the neuro-developmental outcomes of infants exposed to duloxetine via breast milk

Adverse Effects

As a class adverse effects of the SNRIs include:

1. CVS:
 - Palpitations/ tachycardia
 - Orthostatic hypotension
 - Increased BP

- SNRIs have also been associated with **stress-induced (takotsubo) cardiomyopathy.**
- Prolonged QT interval

2. CNS effects:

- Serotonergic effects which occur in children > adolescents > adults.

These may include:

- ♥ Anxiety / agitation
- ♥ Panic attacks
- ♥ Insomnia
- ♥ Tremor

- Seizures:

- ♥ SNRIs may increase the risk of seizures (risk less than with TCAs).

The risk is dose-dependent and is greatest at the start of treatment and when there is a dose increase; use low doses and titrate slowly.

3. **Serotonin toxicity :**

- A more serious serotonin toxicity can develop, particularly when used in combination with other serotonergic agents.

Treatment with either moclobemide or a MAOI (or within 14 days of stopping a MAOI or within 2 days of stopping moclobemide) is contraindicated due to the risk of serotonin toxicity.²

4. Hyponatraemia:

- Usually occurs early in treatment, may be asymptomatic, and is part due to SIADH.
- Treatment with drugs that may cause hyponatraemia may also increase the risk of SNRI-induced hyponatraemia.

5. Sexual dysfunction:

- e.g. impotence, decreased libido

6. Increased suicidal thoughts:

- **Increased** suicidal thoughts and behaviour can occur **soon after** starting any antidepressant, particularly in young people; monitor patients frequently and carefully **early** in treatment.

Dosing²

Using 30 mg once daily for the first week may help reduce nausea and is a suitable starting dose for elderly people.

Depression:

- *Adult*, usual dose 60 mg once daily.

Generalised anxiety disorder:

- *Adult*, initially 30 mg once daily; increase by 30 mg once daily if required, up to a maximum of 120 mg once daily.

Painful diabetic peripheral neuropathy:

- *Adult*, 60 mg once daily.

When ceasing treatment the taper dose over at least 2 weeks, in order to minimise risk of withdrawal effects.



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References

1. eTG - November 2014.
2. Duloxetine in Australian Medicines Handbook Website, Accessed April 2016.
3. Duloxetine in MIMs Website 1 August 2015
4. RWH Pregnancy & Breastfeeding Guidelines, 3 February 2016.

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