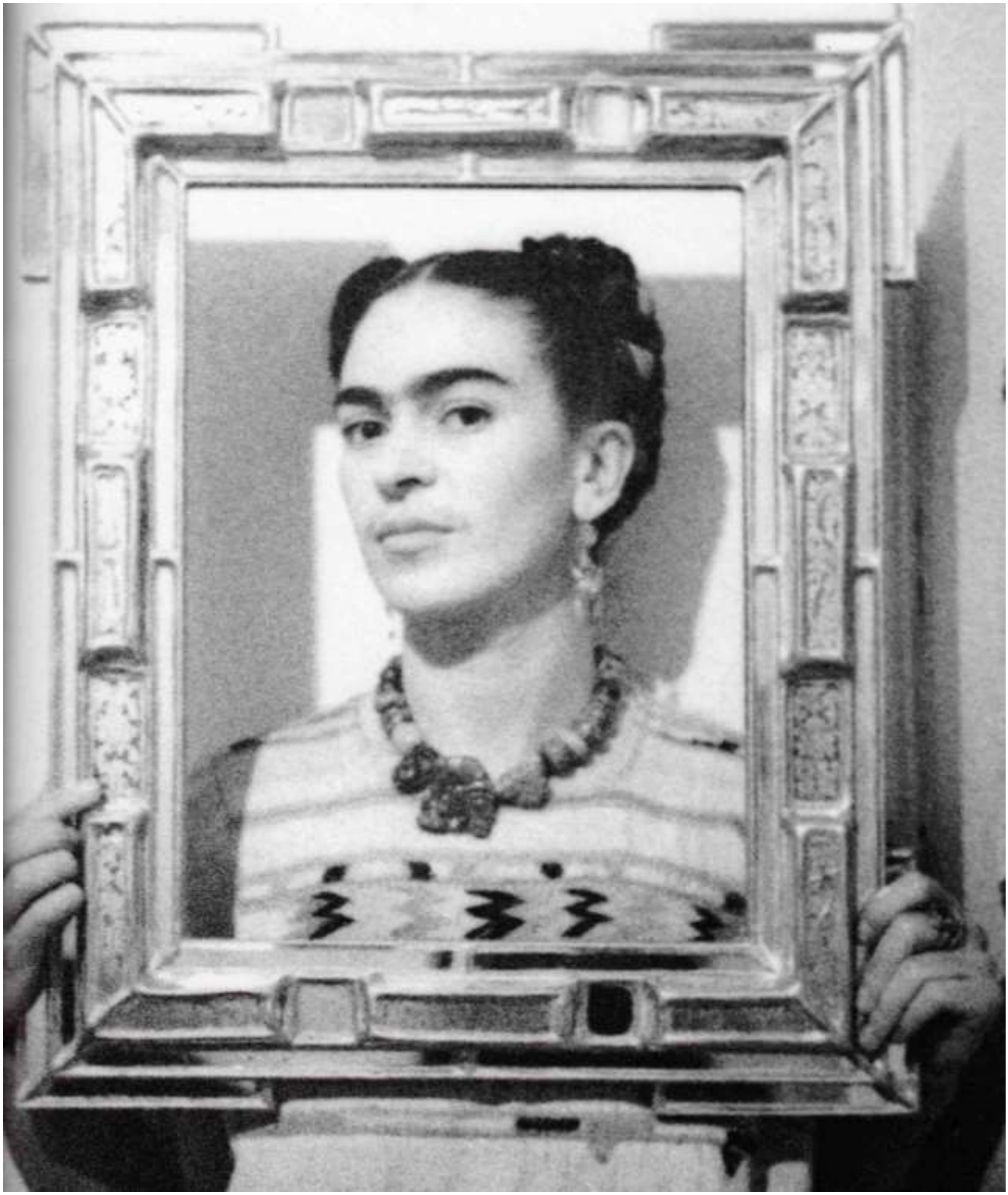
THE NORTHERN HOSPITAL

RIZATRIPTAN



Frida Kahlo with Painted Mirror Frame, c. 1939, (photographed by Nickolas Muray)

"Fulang-Chang and I", oil on masonite, 1937 (assembled after 1939), and framed mirror; Frida Kahlo. (Mary Sklar Bequest), Museum of Modern Art, New York City.

"Conceptual art is made to engage the mind of the viewer rather than the eye.....All of the significant art of today stems from Conceptual art....."

Sol LeWitt.

Frida Kahlo held her first solo exhibition in New York City at the Julien Levy Gallery in November of 1938. Twenty-five of her paintings were exhibited and half of them were sold. It was a major triumph for a first time exhibitor. Frida by this time was known in New York, on account of her visit in 1933 - 1934. But back then she was really only known as "Mrs. Rivera", wife of her famous husband Diego Rivera, the great Mexican Muralist. During her time in New York, she painted alongside her husband, and it was then that her works first caught the public eye. But now Frida was seen as a talented Artist in her own right - not just simply as the wife of Diego Rivera. Her paintings were unique and Art critics and public alike struggled to classify her work. The self-proclaimed "Pope of Surrealism", Frenchman Andre Breton, pronounced her a "self made Surrealist". Although Frida did appreciate the attention and publicity she received

as a result of Breton's commentaries, she always denied she was Surrealist, and on a personal level she detested Breton as a pompous buffoon.

Getting her own exhibition at Levy's Gallery was major coup for Frida. Levy's Gallery, one of the most respected and prestigious in New York City. He was responsible for hosting the first solo exhibitions of numerous important artists during the Depression era, including Alberto Giacometti, Salvador Dalí, and Lee Miller. Breton, wrote an introduction to Frida's work that accompanied the exhibition which was attended by prominent American artists of the time including Georgia O'Keeffe, with whom Frida enjoyed flirting with, and Isamu Noguchi, with whom she had a brief affair. She also had an affair with Julien Levy himself. Levy was an accomplished photographer and he portrayed Frida in famous nude photo-shoot.

Her exhibition was well received by the American Press, even if their praise reflected the sexist and patronizing attitudes prevalent at the time. Time Magazine waxed lyrical about "Little Frida", which annoyed and irritated her. Despite her reservations about Americans in general and her personal revulsion for Andre Breton, she did appreciate the benefits that the exhibition brought to her work. Her affair with Julien Levy, (and possibly Georgia O'Keefe), together with the great success of her New York Exhibition catapulted her onto the world stage as a great up and coming Artist. Frida exhibited 25 paintings at the exhibition, amoung them would become some of her most famous early works, including, Portrait of Luther Burbank, Henry Ford Hospital (with the title "The Lost Desire"), My Birth, My Dress Hangs There, and A Few Small Nips.

Of Frida's extant works, no fewer than around a third are piercing self-portraits, (according to some Art historians up to one half). One appeared in the 1938 exhibition, entitled "Fulang Chang and I". It is not one of her best or most famous works, but it holds a special intrigue for two important reasons. Firstly it is one of her early works that depicts her beloved pets, that would increasingly become the much loved surrogates for the children of her own she desperately craved but could never have, and included, small dwarf deer, spider monkeys, parrots, doves and xoloitzcuintli (small hairless dogs). Fulang Chang was one of Frida's most beloved spider monkeys. Frida stares out back at the viewer, but her expression is somewhat bland and lacks the tortured intensity of her later self-portraits. A purple ribbon, one of her ubiquitous motifs of the universal connectedness of life, binds her to her beloved pet. It embraces both their necks, indicating the closeness of the relationship. This was one work that did not sell, (although Anson Conger Goodyear, the President of MOMA, had wanted to buy it), as Frida gave it as a gift to one of her close American friends Mary Sklar, the sister of the Art historian, Meyer Schapiro, as a gesture of gratitude for a different painting Sklar had purchased from the Levy exhibition.

The second intriguing aspect is that Frida converted this work into one of the earliest examples of Conceptual Art, three decades before this genre emerged in the 1970s and 1980s. The primary idea of Conceptual Art, which evolved over the last quarter of the Twentieth century was to convey a concept, or an idea - the actual quality or execution of the Art work itself was not important. In other words Artistic skill, in the traditional sense was irrelevant, rather it was the clever conveyance of a concept that was the important thing. Conceptual Art was not a single or unified movement as such, rather it emerged

independently in different countries at around the same time, perhaps an almost inevitable consequence of the fantastic radiation of novel genres that characterized the Art of the Twentieth century. Conceptualism had many influences including Dadaism, Expressionism, Abstract Expressionism, Neoplasticism, Color Field Painting, Minimalism and Pop Art amoung others. The idea had become more important that the Art itself and ideas would have their expression in things like "Installations" "Performance Art", and "Land Art"

Frida often gave her self-portraits as gifts - the very first she produced in 1926 she gave to her then boyfriend at the time, Alejandro Gomez Arias. Later she presented one as a birthday present to none other than Leon Trotsky. Giving self-portraits was not unusual for Frida, however, the inclusion of a mirror to go with it most definitely was! Frida told her friend Mary to hang the mirror beside her portrait so that whenever she looked at it she would also see an image of herself in the mirror, creating a double image, enabling them to always be together. It was a charming, personal, creative and loving touch. The idea - the Concept - was more important than the bland portrait itself.

The mirror also held a special personal poignancy for Frida. She first began painting while convalescing from a horrific bus accident, that almost claimed her life at the age of just eighteen years, and had left her with lifelong deformities, chronic pain, and a tragic inability to bear children. She spend many months immobilized in full body plasters recovering from her terrible injuries. The only way she could learn to paint from books or to produce self portraits was by the use of elaborate set ups of mirrors. She always held an image in her mind of her own face in mirrors, and an inner agony, sadness and stoicism would be engrained in all her future self-portraits. One of Frida's most prolific photographers, Lola Alvarez Bravo, who photographed her throughout her life, observed that "Frida lived surrounded by mirrors." She even had one attached to her canopy bed. It was her method of deep, unrelenting and life-long self reflection, an obsession perhaps matched only by the great Rembrandt van Rijn.

Today Frida Kahlo's "Fulang Chang and I" together with the matching mirror she sent to her friend Mary Sklar, resides in the Museum of Modern Art, in New York city, where admirers flock to take photographs of themselves alongside one of the Twentieth century's most famous Artists. You look at her, looking at a reflection of herself. Then you turn your head and see yourself as the viewer in contemplation. It is as if you are trapped with Frida within a higher dimensional world of images reflected and re-reelected over and over in infinite iteration just as when two mirrors are placed directly opposite each other. Mirrors were a powerful motif for Frida. "Fulang Chang and I" is a proto-work of Conceptual Art.. The great Conceptual Artist Sol LeWitt once wrote, "Ideas alone can be works of Art; they are in a chain of development that may eventually find some form, (but) all ideas need not be made physical".

Frida Kahlo's contemporaries struggled to understand her work, even though they were enthralled and captivated by it. Officially she was called a "Surrealist" but she always rejected this label, claiming she was in fact a "Realist". Art commentators today sometimes designate her a "Magic Realist", however Frida would not have agreed, as she rejected all labels. "I do not paint dreams," she once exclaimed. Nor did she paint meaningless "magic". In truth Frida Kahlo had her own unique style, an amalgam of

Native American Mythology and Christian symbolism expressed in a language of unique and deeply personal motifs subsumed within novel elements unknown to her contemporaries that were decades ahead of her time.

Frida Kahlo's "Fulang Chang and I" is a charmingly brilliant work of early Conceptualism. It shows some of the usual motifs of her deeply reflective self-portraits, however rather than feeling a cold and distant detachment from these haunting works, in this case Frida, by use of her accompanying mirror reaches out to the viewer in a unique way. By the viewer observing her or his own reflection alongside Frida's a warm sense of intimacy with the Artist may be experienced.

Frida Kahlo's self-portraits, may at a first superficial glance seem to all follow much the same plan - but this is to misunderstand the important differences that make each work quite unique when examined in a more informed manner.

In the host of the triptan anti-migraine agents, one may be tempted to dismiss Big Pharma's propensity for "me too-ism". The portrait of any one of them gives much the same initial impression as any other. However a more informed knowledge of these portraits shows that some do in fact have important differences. Rizatriptan for example has a formulation that actually takes into account that not all migraine suffers are the same. A wafer formulation exists that reaches out to those who suffer from terrible nausea and vomiting, enabling them to absorb the agent from the tongue. It is a variant that more directly engages the patient as a unique individual!

A Frida Kahlo admirer at MOMA, spends a quiet moment with the Artist..

RIZATRIPTAN

Introduction

Rizatriptan is a highly specific **5-HT$_1$** receptor **agonist** with particular affinity for the **5-HT$_{1B}$** and **5-HT$_{1D}$** receptors.

Serotonin is **5-hydroxytryptamine** (**5-HT**) which is a monoamine neurotransmitter that is derived from tryptophan.

Rizatriptan a **specific** agent for the treatment of migraine headache.

It is (along with other triptans) therefore the most specific treatment for both migraine and cluster headaches.

The triptans have a number of important advantages over many other anti-migraine medications including:

1. They are not significantly sedating, (unlike chlorpromazine)

2. They do not cause hypotension (unlike chlorpromazine)

3. They are more efficacious agents (providing true migraine is the cause of the headache), than the simple analgesics or prochlorperazine.

4. They do not have physical or psychological addictive potential.

5. They are a **specific** treatment for migraine.

6. They alleviate the non-headache features of migraine (e.g. nausea and vomiting). (ergot does not).

7. They can be used effectively at any point in the migraine, (compared to ergot which must be used early)

Rizatriptan is available in two forms:

1. Regular tablets for swallowing

2. Orally disintegrating tablets (or "**wafers"**)

    - The **wafer formulation** can be taken *without water* and so is particularly useful in patients with significant nausea / vomiting.

Rizatriptan has similar efficacy to **sumatriptan.**

History

Studies in the 1960s showed that vasoconstriction from serotonin (5-HT), ergotamine and noradrenaline could reduce migraine attacks. Research also showed that platelet 5-HT levels are reduced during migraine attacks.

As 5-HT had too many adverse effects to be used as a drug, research was commenced on the receptors of 5-HT in order to discover and develop more specific agonist agents for 5-HT receptors.

Sumatriptan was the prototype serotonin agonist and was introduced in the Netherlands in 1991 for the treatment of migraine headache.

Rizatriptan was introduced into clinical practice in the United States in 1998.

Chemistry

Rizatriptan is a synthetic **triptan** (i.e. tryptamine based) drug.

Tryptamine is a monoamine alkaloid that contains an indole ring structure, and is structurally similar to the amino acid tryptophan, from which it derives its name.

Physiology

See Appendix 1 below.

Classification

The triptan anti-migraine serotonin agonist drugs currently available in Australia include:

1. Sumatriptan
2. Eletriptan
3. Naratriptan
4. **Rizatriptan**
5. Zolmitriptan

Note that there is no evidence that any triptan is more effective than another nor safer than any another.

The response to each agent however can vary considerably between individual patients.

The same individual may also respond quite differently to different triptans, and so if one agent is ineffective, a trial of a different triptan is worthwhile.

Preparations

Rizatriptan benzoate as:

Regular tablets:

- 10 mg

Wafers (i.e orally disintegrating tablets):

- 10 mg

Mechanism of Action

Triptans are specific and selective agonists for the 5-HT_1 receptors.

Rizatriptan is a highly specific **5-HT_1** receptor **agonist** with particular affinity for the **5-HT_{1B}** and **5-HT_{1D}** receptors.

Rizatriptan has no clinically significant activity at 5-HT2 or 5-HT3 receptor subtypes

Zolmitriptan, Rizatriptan, Naratriptan, Almotriptan, and Frovatriptan bind to 5-HT_{1B} and 5-HT_{1D} receptors and Eletriptan binds to 5-HT_{1B} , 5-HT_{1D} and 5-$HT1_F$ receptors.

The vascular $5HT_1$ receptor is found predominantly in cranial blood vessels and mediates vasoconstriction. The carotid arterial circulation supplies blood to the extra-cranial and intra-cranial tissues such as the meninges. Dilatation in these vessels is thought to be the underlying mechanism of migraine. Initial aura has been attributed to an initial vasoconstriction phase, that precedes the vasodilation or headache, phase.

Triptans are believed to exert their effects through vasoconstriction of cranial vessels by acting selectively at the $5HT_{1B}/_{1D}$ receptors.

They are also thought to inhibit the abnormal activation of trigeminal nociceptors.

Pharmacodynamics

With the exception of naratriptan, the oral triptans relieve headache within **30 - 60 minutes.**

Rizatriptan has similar efficacy to **sumatriptan.**

It is more effective the earlier it is given following the onset of headache, however it can still have good efficacy if given late.

Eletriptan, naratriptan, rizatriptan and zolmitriptan have better oral bioavailability than sumatriptan, however this difference may not be clinically significant if adequate doses are given. [1]

The response to each agent can vary considerably between individual patients.

The same individual may also respond quite differently to different triptans, and so if one agent is ineffective, a trial of a different triptan is worthwhile.

Pharmacokinetics

Absorption:

- Rizatriptan tablets are rapidly and well (90%) absorbed from the gastrointestinal tract following administration.

  They have an absolute bioavailability of around 47% owing to a moderate first-pass metabolism

  The rate of absorption of the wafer is somewhat slower than the regular tablet formulation.

Distribution

- Rizatriptan is only minimally bound to plasma proteins at around 14 %.
- The volume of distribution is approximately 140 litres in males and 110 litres in females.
- It is unknown whether rizatriptan crosses the human placenta.
- It is likely that rizatriptan is distributed into human breast milk.

Metabolism and excretion:

- The primary route of rizatriptan metabolism is via oxidative deamination by **monoamine oxidase-A (MAO-A)** to the indole acetic acid metabolite, which is not pharmacologically active.
- The plasma half-life of rizatriptan is around 2-3 hours.

Indications

The triptans as a class are indicated for:

1. The acute relief of migraine headache (with or without aura).
2. The acute relief of cluster headache

They are not effective for other forms of headache.

Contra-indications/precautions

Contraindications / precautions to the triptans as a group include:

1. CVS disease:

   Triptans should not be used in:

   - Ischaemic heart disease
   - Prinzmetal's angina
   - Uncontrolled hypertension.

2. Cerebrovascular disease:

   - TIA
   - Stroke

3. Hemiplegic migraine:

   - Although there is no good information on the use of triptans in hemiplegic migraine, current convention is that in true hemiplegic migraine (i.e attacks of organic hemiplegia), they are avoided.

     Note that it is safe to use if there is just sensory deficit or mild "heaviness" of limbs on one side, as opposed to true hemiplegia.

4. Drug interactions:

   - Use with, or within **14 days** of stopping, a **MAOI**:

     ♥ These inhibit the metabolism of sumatriptan, and so may increase toxicity.

     Eletriptan and **naratriptan** are the only triptans that are **not** substrates of MAO−A so these are the best options in patients taking MAOIs.

   - Use with, or within **24 hours** of stopping, **ergometrine** or **methysergide:**

     ♥ Ergometrine may increase risk of vasospasm.

- ♥ Methysergide (an ergot alkaloid derivative) may increase the risk of vasospasm with triptans

- Use with ondansetron/ granisetron

  On theoretical grounds it may be expected that ondansetron (or similar) as a serotonin antagonist could reduce the effects of triptans, which are serotonin agonists.

  While - strictly speaking - they act on different serotonin receptors; ondansetron being a highly selective **5-HT$_3$** serotonin receptor **antagonist**, whilst triptans are highly specific **5-HT$_1$** receptor **agonist**, receptor specificity is probably not completely exclusive to these receptors groups.

  In any case, anecdotally, they have often been used together with apparently good effects of both agents, (*personal communication Dr Doug Crompton 25/8/2016*).

5. Severe hepatic impairment.

6. Elderly:

   - Data is limited; but use not recommended due to potential increased risk of cardiovascular adverse effects.

Pregnancy

Rizatriptan is a category B1 drug with respect to pregnancy.

Category B1 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 not shown evidence of an increased occurrence of fetal damage.

According to the post-marketing Pregnancy Registry, the use of rizatriptan has not been associated with an increased risk of major malformations.

Most of the information on triptan use during pregnancy is available specifically for sumatriptan. Maternal use of sumatriptan for the treatment of migraines has not been associated with an increased risk of congenital malformations. Further studies are needed to confirm the safety of other triptans in pregnancy.

One study has suggested there may be a possible increased risk of preterm birth and low birth weight with exposure to triptans during pregnancy. Another study has reported triptan use during the second and/or third trimesters may be associated with a slight increase in the risk of atonic uterus and haemorrhage during labour.

Analgesics such as paracetamol or opioids (e.g. codeine, morphine) are the initial medicines of choice to manage migraine attacks during pregnancy.

Breast feeding

Published reports following rizatriptan use during breastfeeding have not been located.

Consider an alternative medicine with greater clinical safety information during breastfeeding if possible.

If a triptan is the treatment of choice, consider sumatriptan, as it has been most studied.

Use sumatriptan at the lowest effective daily dose and observe the breastfed infant for potential adverse effects such as drowsiness, vomiting, poor feeding and restlessness.

Adverse Effects

Adverse effects are usually minor.

Possible adverse effects of the triptans, as a group include:

1. Mild dizziness

2. Mild sedation

3. A "rush" or 'flushed" feeling - more common with SC administration of sumatriptan

    - Also described are subjective feelings of chest "tightness" (without any documented changes in lung function or on ECG)

4. Mild elevations of blood pressure.

5. Serotonin toxicity:

    - There have been reports of triptans causing serotonin toxicity, but the risk is very low.

      It may be more likely to occur when sumatriptan is combined with other serotonergic agents.

6. Coronary vasospasm.

    - Therefore is best avoided in patients with significant coronary artery disease.

Dosing

Usual adult dosing is:

- Oral, 10 mg as soon as possible after onset of headache

  If migraine recurs a second dose can be taken, 2 hours after the original dose.

  The maximum daily dose is **30 mg**.

The **wafer formulation** should be placed on top of the tongue and kept there while it dissolves. dissolves. Water does not have to be taken with the wafer, however if the patient is able to take water, then it may be absorbed more quickly.

Appendix 1

5-Hydroxy-tryptamine receptor subtypes:

5 HT Family	Receptor Type	Mechanism	Action
5 HT_1 ***Subtypes:*** **1A, 1B, 1D, 1E, 1F**	G_i/G_o-protein coupled.	Decreasing cellular levels of cAMP.	Inhibitory
5 HT_2 ***Subtypes:*** **2A, 2B, 2C**	G_q/G_{11}-protein coupled.	Increasing cellular levels of IP_3 and DAG	Excitatory
5 HT_3	Ligand-gated Na^+ and K^+ cation channel	Depolarizing plasma membrane.	Excitatory
5 HT_4	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5 HT_5 ***Subtypes:*** **5A, 5B**	G_i/G_o-protein coupled	Decreasing cellular levels of cAMP.	Inhibitory
5 HT_6	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory
5 HT_7	G_s-protein coupled.	Increasing cellular levels of cAMP.	Excitatory

There is no 5-HT_{1C} receptor, as it was reclassified as the 5-HT_{2C} receptor

The Works Exhibited by Frida Kahlo at her first solo exhibition, at Julien Levy's Gallery, in New York City, 1938:

1. *Portrait of Luther Burbank*
2. *Henry Ford Hospital (with the title "The Lost Desire")*
3. *My Birth*
4. *My Dress Hangs There*
5. *A Few Small Nips (with the title "Passionately in Love")*
6. *I belong to My Owner*
7. *Self Portrait Dedicated to Leon Trotsky (with the title "Between the Curtains")*
8. *My Nurse and I*
9. *Memory (with the title "The Heart")*
10. *Fulang-Change and I*
11. *The Airplane Crash (with the title "Survivor")*
12. *Still Life with Pitahayas*
13. *The Fruits of the Earth*
14. *Xochítl*
15. *Self Portrait "The Frame", (later sold to the Louvre)*
16. *Self Portrait with Itzcuintli Dog*
17. *They Asked for Planes and Only Got Straw Wings*
18. *Remembrance of an Open Wound*
19. *The Four Inhabitants of Mexico (with the title "The Square is Theirs")*
20. *Girl with Death Mask (with the title "She Plays Alone")*
21. *What the Water Gave Me*
22. *Eye*
23. *Tunas*

24. *The Deceased Dimas (with the title "Dressed Up for Paradise")*

25. *My Grandparents, My Parents and I (with the title "My Family")*

References

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