

SELECTIVE SEROTONIN RE-UPTAKE INHIBITOR OVERDOSE



"Peonies", oil on canvas 1887, Charles Edward Perugini.

“...the fair Honoria had no sooner attained the sixteenth year of her age than she detested the importunate greatness which must forever exclude her from the comforts of honourable love; in the midst of vain and unsatisfactory pomp Honoria sighed, yielded to the impulse of nature, and threw herself into the arms of her chamberlain, Eugenius...”

*Edward Gibbon, The History of the Decline and Fall of the Roman Empire,
Volume 3, 1781.*

“Caught in a clandestine affair with a certain Eugenius.....He was executed for the crime, and she was betrothed to Herculanus, a man of consular rank and of....good character. (In response) she sent the eunuch Hyacinthus to Attila offering him money to avenge her marriage. She also sent her ring as her pledge to the barbarian.....”

Priscus 5th Century A.D

In 450 A.D the Western empire stood on the edge of the abyss. The enemy was at the gate, and it was unlike any Rome had faced before, a ferocious horde of uncertain origin from the East that had first appeared in the late Fourth century A.D. Over the next three generations they had swept through the lands of Germania in the north, sweeping away all who stood in their path. Increasing numbers of northern barbarian tribes sought refuge within the lands of the Roman empire. They brought with them terrifying stories of a scarcely human race of invaders from the further reaches of the Silk Road. Incredibly skilled riders, and able to use the bow at full gallop with ease, in battle they appeared invincible. Their leader, Attila, had a fearful reputation, and now having conquered a vast swathe of the Hercynian barbarian homelands, he stood at the Rhine and looked with envious eyes on the Western empire - and all this had come to pass on the folly of a young Princess of Rome, named Honoria.

Some years previously a great scandal had erupted in the Royal house. The Princess Honoria, at the age of just sixteen years was by all accounts precocious and uncontrollable. Unable to abide by the stifling protocols of the court, she flung herself into an affair with her chamberlain, an obscure man by the name of Eugenius. Her mother, Placidia regent of the Western Empire and so de facto ruler of it, in the name of her small son Valentinian III, found out about the affair. In an ungoverned fury, she had the hapless Eugenius executed, then to keep a reign on her delinquent daughter arranged for her marriage to an older, insipid, but respectable senator by the name of Herculanus, who was deemed to have no aspirations towards the throne whatsoever. Horrified at this prospect Honoria decided to take matters into her own hands. She knew and had seen how prominent Romans had employed the services of savage barbarians to threaten their personal enemies. Honoria would take this strategy to an new and alarming extreme - she would appeal to no less a barbarian, than Attila himself!

She sent a secret messenger, the eunuch Hyacinthus, to the barbarian king, offering him a vast amount of gold to demand that Placidia restore her daughter to the title of Augusta and to break off her unwanted marriage. It was usual practice among high-born Romans to send a valuable personal item with secret messengers in order to provide proof of their important identity as well as to prove that the bearer was acting on their behalf. Honoria made a fateful choice in more ways than one - she chose as her

identifying sign, a magnificent jeweled ring. Honoria was to be disappointed however. Instead of getting Attila to make war like threats for her engagement to be annulled, he immediately declared actual war! Attila was beside himself. He had taken the ring not as an identifier, but rather as a proposal of marriage! He had thought long and hard about whether to attack the Western Empire or the Eastern. The East was militarily strong while vast swathes of the West were by this time populated with barbarian "gatecrashers" of uncertain loyalties. Honoria's "marriage proposal" finally convinced Attila, if indeed he needed any further convincing at all, to attack the West. Tired of receiving "tribute" from Constantinople, for his quiescence, he wanted an excuse to attack. Excited at the prospect of becoming the new Emperor of the West, and even more excited at the prospect of marrying a Princess of Rome, he led his vast horde across the Rhine into Gaul.

In great alarm Placidia consulted the Eastern Emperor Theodosius as to what should be done. Theodosius was blunt in his reply. He did not want war with Attila, Honoria should be handed over to the Huns! Placidia, as much as she probably thought about it, could not bring herself to hand her daughter over to a brute savage and so not knowing what to do, had her locked up in a convent instead. Just at this very point reports began to come in from Constantinople that the senior Emperor had fallen off his horse and had been killed! The only surviving male member of the house of Theodosius was now Placidia's ineffectual son Valentinian III. At that moment he had become the sole ruler of the entire empire, East and West. The coming battle with Attila would now decide the fate not only of the West, but of the entire Roman world! Placidia had only one chance - she would turn to two of the most gifted men in the West, the diplomat Avitus and the greatest general of the age, a man she despised, Aetius. Young Honoria had engineered quite a situation!

When we assess our patients who have overdosed on SSRIs, we need recall the lessons of the story of Attila and the Princess Honoria! We must not make assumptions! Honoria had assumed that Attila would merely make forceful threats and be happy with his gold. Attila on the other hand assumed that Honoria had fallen in love with him! Disastrous consequences all round! Whilst it is quite true that the great majority of SSRI overdoses are benign, we must not assume that all will be well. If the agents taken happen to be either citalopram or escitalopram the situation may not be so benign - and if other undisclosed serotonergic agents have been coingested then the situation can potentially be alarming! There must therefore be no casual assumptions! Careful enquiry must always be made, not only in the case of SSRI overdose, but in any overdose in general, of the possibility serious coingestion.

SELECTIVE SEROTONIN RE-UPTAKE INHIBITOR OVERDOSE

Introduction

SSRI overdose is common. The clinical course is usually benign.

Mild serotonin syndrome may occur in some patients.

More severe serotonin syndrome presentations are unlikely unless there is **co-ingestion of other serotonergic drugs**.

Citalopram and **escitalopram** appear unique in their ability to cause **dose-dependent QT prolongation**. These agents are also the most likely to cause **seizures**.

Note that SSRIs are not the same thing as SNRIs, (which are far more toxic).

See also separate document on Serotonin Toxicity (in Toxicology folder).

Preparations

Current agents include:

- Citalopram ● Escitalopram ● Fluoxetine
- Fluvoxamine ● Paroxetine ● Sertraline

Pharmacokinetics

Absorption:

- All are rapidly absorbed.

Distribution:

- They are protein bound with large volumes of distribution.

Metabolism and excretion:

- They undergo hepatic metabolism to lesser active metabolites which are excreted by the kidneys.
- Elimination half-lives are approximately 24 hours.

Pathophysiology

The SSRIs selectively inhibit central serotonin re-uptake.

These agents have little affinity for other receptors including, adrenergic, cholinergic, dopaminergic, serotonergic or histamine receptors.

Risk Assessment

Many cases will remain asymptomatic.

Mild symptoms of serotonin syndrome will occur in less than 20% of cases, and if they occur usually last < 12 hours.

More severe or even *life threatening* cases of serotonin syndrome is far more likely if there has been *co-ingestion* of other serotonergically acting drugs (particularly if acting via a different mechanisms) such as:

- Tramadol
- MAO inhibitors:
 - ♥ This combination especially may lead to severe and life-threatening serotonin toxicity.³
- Selective noradrenaline reuptake inhibitors (venlafaxine/ bupropion)

Risk of seizures:

These are uncommon, but when they do occur, they are most commonly associated with citalopram and escitalopram.

They can be seen with more severe serotonin toxicity in general, with coingestion of other serotonergic agents.

Risk of QT prolongation:

Citalopram and escitalopram have the unique ability to cause a dose dependent prolongation of the QT interval.

The risk of **QT prolongation** is increased with doses of:

- **Citalopram > 600 mg**
- **Escitalopram > 300 mg.**

Actual arrhythmia (torsades des pointes) however, is fortunately rare.

Clinical Features

Symptoms usually begin within 4 hours of ingestion and resolve within 12 hours.

1. Nausea is common.
2. Mild serotonergic symptoms:

The commonest symptoms being:

- Anxiety
- Tremor
- Tachycardia or bradycardia
- Mydriasis
- Sweating

Note that coma or significant depression of conscious state is *not* due to SSRI overdose in isolation and will indicate co-ingestion and/ or secondary complication.

3. Moderate to severe serotonin toxicity:

- This may be seen if there is **co-ingestion** of other serotonergic agents.

See also separate document on Serotonin Toxicity (in Toxicology folder).

4. Seizures

- May *uncommonly* occur and are usually self-limiting.
- Citalopram and escitalopram are the agents that most commonly causes seizures.

Seizure onset is heralded by serotonergic symptoms:

- Tachycardia
- Anxiety
- Sweating
- Tremor
- Mydriasis

5. Cardiovascular:

- Prolonged QT and arrhythmias are uncommonly seen with citalopram and escitalopram overdose.

Investigations

1. FBE
2. U&Es/ glucose
3. Consider the possibility of co-ingestants, blood alcohol and paracetamol levels.
4. ECG:
 - Check **QT intervals**, particularly in the case of citalopram or escitalopram.

Use the Drug Induced QT prolongation nomogram to assess risk, (see **Appendix 1 below**).

Monitoring should continue for at least **8 hours** post ingestion and until risk resolves according to the nomogram.

Management

1. Attend to any immediate ABC issues.
 - IV access

Cardiac monitoring:

 - This should be done for citalopram and escitalopram overdoses.
2. Anxiety or delirium:
 - Treat with titrated IV diazepam to clinical effect.
 - Note that increasing signs of serotonin toxicity may herald the onset of seizures and **5 mg IV diazepam** (repeated as required 2-5 minutely) is recommended to prevent these.
3. Seizures:
 - Treat with IV diazepam.
4. Charcoal:

- This is not necessary in cases of SSRI overdose unless **citalopram** ($> 600\text{mg}$) or **escitalopram** ($> 300 \text{ mg}$) has been taken where it may be given to alert and co-operative patients within **4 hours** of ingestion.

5. Serotonin syndrome:

- **For more serious cases of serotonin syndrome, see separate serotonin toxicity document.**

Disposition:

All patients with SSRI overdose (apart from **citalopram** or **escitalopram**) should be observed for a minimum of 6 hours.

After this time if they are symptom free with a normal ECG they may be medically cleared.

Patients who have taken **citalopram** or **escitalopram** will require a longer period of continuous ECG monitoring and serial ECGs.

Monitoring should continue for at least:

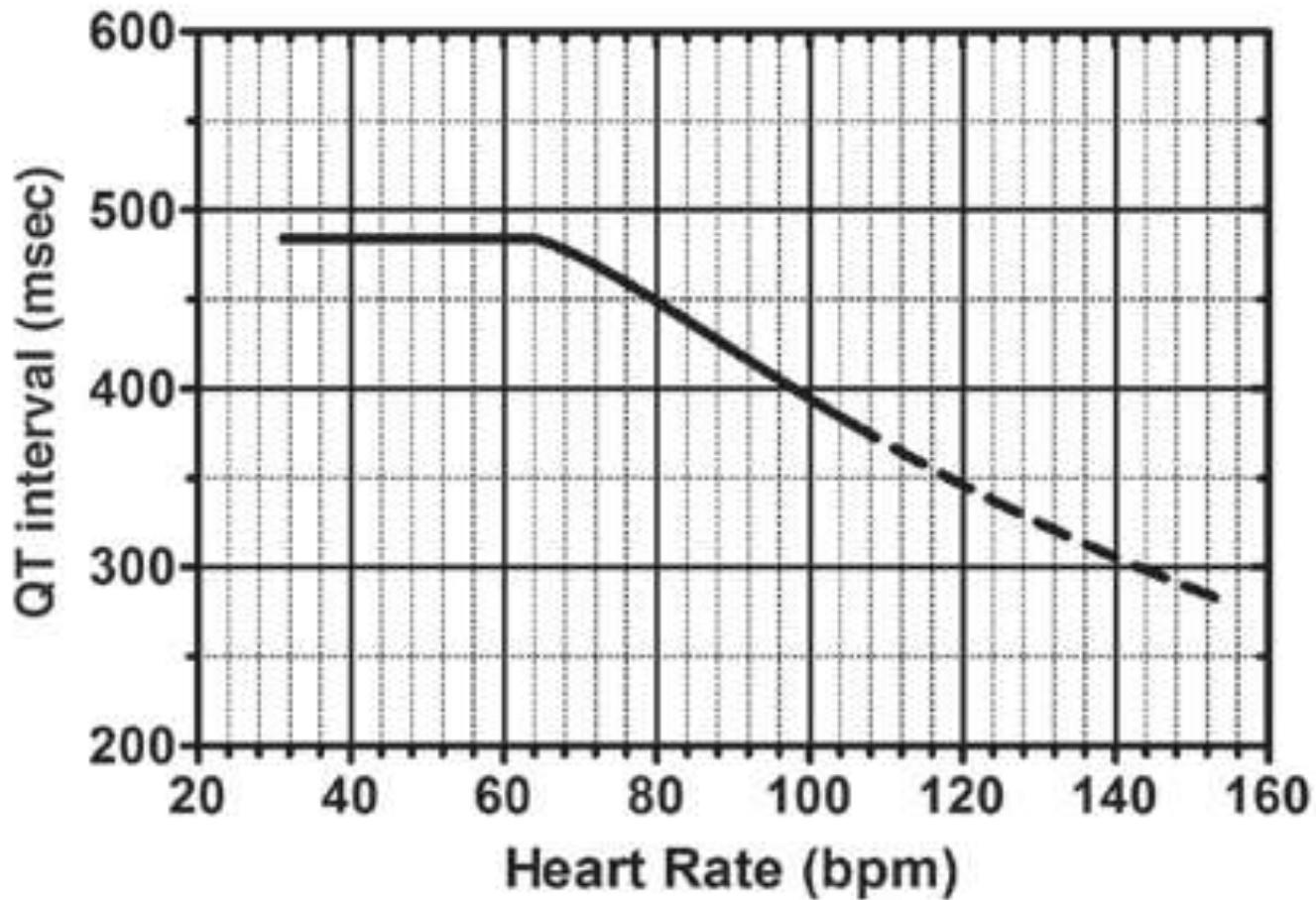
- **8 hours** if:
 - ♥ 600 mg - 1000 mg of citalopram has been ingested
 - ♥ 300 mg - 500 mg of escitalopram has been ingested
- **12 hours** if:
 - ♥ $> 1000 \text{ mg}$ of citalopram has been ingested.
 - ♥ $> 500 \text{ mg}$ of escitalopram has been ingested.

and then till any ECG changes have resolved.

Any patient who develops severe serotonin syndrome will require admission to HDU/ICU.

Appendix 1

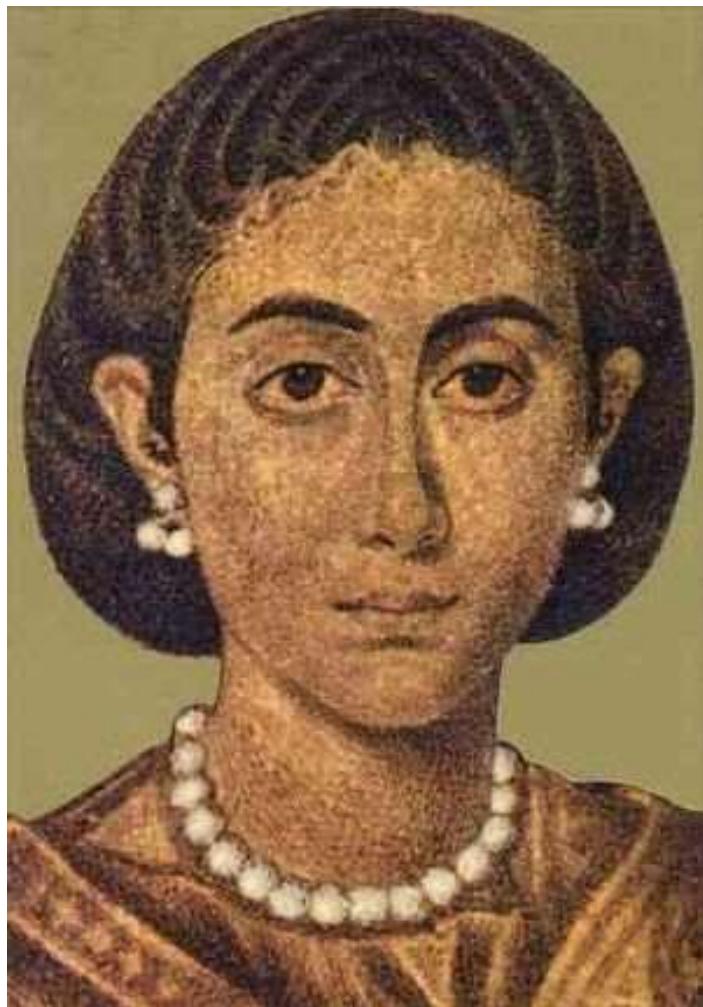
The QT Nomogram²



Solid line indicates heart rates that are not tachycardic

Dashed line is extrapolated to allow assessment of faster heart rates

The QT nomogram is a plot of the QT interval versus the heart rate. A QT-heart rate pair above the line is associated with an increased risk of torsades de pointes.



Aelia Galla Placidia, mother of Honoria and the boy Emperor Valentinian III, regent and de facto ruler of the Western Empire, 425 - 450 A.D. Roman Fresco, early Fifth century A.D.

References

1. SSRIs in L Murray et al. Toxicology Handbook 3rd ed 2015.
2. Geoffrey K Isbister; Risk assessment of drug-induced QT prolongation Aust Prescr 2015; 38:20 - 4.
3. eTG - March 2015.

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