

RISPERIDONE



“Woman Looking Through Opera Glasses”, oil on cardboard c. 1869 - 77, Edgar Degas, Galerie Neue Meister, Dresden.

"I do not like carriages. One sees no one. That is why I love the omnibus. One can observe the people. We were created to observe one another...."

Edgar Degas.

Edgar Degas was an intense observer of people. His most famous works record the everyday lives the citizens of Belle Epoch Paris. His subjects were mostly women, among his favoured were the milliners, the washerwomen, the night café singers, prostitutes and circus performers, but by far his most prolific and most famous images were those of the dancers of the Paris Opera and more intimately, even shockingly for the times, women at their bath. He depicted his women as though observing them without their knowledge, and inevitably with regard his bathers, he drew heated accusations of "keyhole voyeurism". "We were created to observe one another....", he once famously quipped; by what he really meant was that he was created to observe others; not the other way round. Or so it would seem for any who know his work, however this is not entirely correct. There exists a remarkable, largely unknown set of works, that can be counted on just one hand, where Degas himself seems the object of scrutiny! Of course he did many portraits, whose subjects, by definition look back at the viewer, however these are in a the detached manner of portraits in general. But these few works are strikingly different to any normal portrait - the microscope, or in these cases the opera or field glasses are very much focused back onto the individual viewer in a palpably uncomfortable manner.

Only four such works are known, or at least have survived. They show a recurring motif of a mysterious woman spying back at the viewer through opera glasses. These enigmatic works, of a model unknown, are generally dated to the mid 1870s, however, the eminent Art historian and Degas expert, Henri Loyrette, suspects, they were actually produced earlier in the late 1860s. Loyrette convincingly traces back the origin of the works to a sketch Degas did of his sister, Marguerite around 1860 to 1862, now residing in the Bibliothèque Nationale de France. Marguerite stares intensely and directly back at the viewer, her left arm folded across her chest, her right, held up to her face with thumb supporting her chin and fingers framing her right cheek and eye. This image is next encountered in another small sketch, now in the British Museum, circa 1868, of a woman looking through opera glasses back at the viewer. The general pose is strikingly similar to the earlier portrait of Marguerite. We know that Degas kept countless sketches to use for future templates for works he would produce in his studio, sometimes many years later. Then around 1869 are two beautiful unfinished oils of a woman, one now in Dresden, the other in Glasgow, who, in exactly the same motif as the British Museum sketch, stare directly back at the viewer through field glasses.

Another less well known motif of Degas' was his scenes of horse racing, a sport that had relatively recently been imported from England and enthusiastically taken up by Parisians, including no less a personage than the emperor Napoleon III himself, who became a great patron of the new sport. Degas in his earlier years loved to attend the grand racing gatherings where he could observe not so much the event itself but the people and the jockeys as they prepared for a race. And it is in one of his less well known racing works we finally see the appearance in a finished work of the mysterious woman with the field glasses. In "Jockey's at the Racecourse", c. 1872. Like many of his earlier works at the Paris Opera, before his attention turned definitively to the dancers

themselves, the striking focus of the work is not the jockeys themselves but an elegantly dressed couple who have come to view the race. The woman however, has no interest in the jockeys at all - rather she focuses her field glasses directly back at Degas himself - the observer of human nature, is himself observed!

After the appearance of "Jockey's at the Racecourse", c. 1872, we never again see Degas as the observed; rather it is he who observes others, who are unaware of his scrutiny. His abrupt abandonment of the brief motif of the woman with the field glasses, perhaps reflected his own discomfort at being put into the spotlight - "I would like to be famous....and unknown" he once wrote.

Edgar Degas, of course was not alone in his aversion to intense scrutiny, even though he was perfectly happy to inflict this onto unsuspecting others. In patients with psychotic illness, a major symptom can be an overwhelming sense of being watched, by imagined persons or demons of ill intent. When Edgar became uncomfortable with his mysterious woman who watched him through binoculars, he simply shrugged his shoulders, abandoned the motif and eagerly turned his own binoculars back onto women at their bath! It is not such a simple thing however, for those who cannot so readily switch off their imagined demons; they are ever lurking in the background, behind half closed doors, under the bed or just around the next corner. Fortunately 21st century medicine provides these tormented souls with an array of soothing newer generation, antipsychotic agents, such as risperidone.



Left: Marguerite Degas, soft-ground etching and drypoint, c. 1860-62. Edgar Degas. Bibliothèque Nationale de France. Right: Young woman with field glasses, essence on pink paper, c. 1868, Edgar Degas, British Museum.

RISPERIDONE

Introduction

Risperidone (trade name “**Risperdal**” in Australia) is a second generation (or “atypical”) antipsychotic agent.

It is as effective as any of the newer antipsychotic agents and has far less (if any) extrapyramidal side effects that are characteristic of the older agents.

It is effective in the treatment of both the “**positive**” and “**negative**” symptoms of schizophrenia.

See also separate documents on:

- **Risperidone Overdose (in Toxicology folder).**
- **Dystonic Reactions (in Toxicology folder).**

History

Chlorpromazine was developed in 1950. It was the first drug developed with a specific antipsychotic action and served as the prototype of the phenothiazine class of antipsychotic drugs that followed it.

The introduction of chlorpromazine during the 1950s into clinical use for schizophrenia and acute psychoses represented a significant advance in the history of psychiatry.

The “atypical” or second generation antipsychotics were developed and introduced into clinical practice during the 1990s. Olanzapine, **risperidone**, and quetiapine were introduced initially while ziprasidone and aripiprazole came onto the market in the early 2000s.

Chemistry

Risperidone belongs to a new class of antipsychotic agent, the **benzisoxazole derivatives**.

Classification

There is no formal classification of the antipsychotic agents, however by tradition they are loosely divided into two principal groups.

1. The older “**first generation**” or “**typical**” group.
2. The newer “**second generation**” or “**atypical**” group.

In general the second generation agents have significantly less adverse effects profiles such as sedation, extrapyramidal side effects, anticholinergic effects or the

development of neuroleptic malignant syndrome. The risk of these particular adverse effects although small is not completely eliminated with the second generation agents.

It has also been claimed that the second generation agents are more effective against the “negative” symptoms of schizophrenia, but this has *not* been convincingly proven as a *class* effect.

It should be noted that designating antipsychotics as first generation and second generation may be of limited value as it probably exaggerates the differences between groups and overstates similarities between members within each group. On this basis some prefer not to use this classification; nonetheless the terminology remains widely used.

First Generation Antipsychotic Agents :

These fall into two major groups:

1. **Phenothiazines:**

- *Lower potency:*
 - Chlorpromazine.
 - Pericyazine.
 - Thioridazine.
- *Higher potency:*
 - Fluphenazine.
 - Flupenthixol
 - Prochlorperazine
 - Trifluoperazine.
 - Zuclopenthixol

2. **Butyrophenones:**

- Droperidol.
- Haloperidol.

Second Generation Antipsychotic Agents:

These include:

1. Amisulpride
2. Aripiprazole
3. Asenapine
4. Clozapine
5. Olanzapine
6. Paliperidone
7. Quetiapine
8. **Risperidone**
9. Ziprasidone

Preparation

Tablets (standard release):

- 500 micrograms, 1 mg, 2 mg, 3 mg, 4 mg,

Liquid:

- Oral liquid, 1 mg/mL, 100 mL

Ampoules, (as extended release microspheres for long acting depot injection):

- 25 mg, 37.5 mg, 50 mg; (all as powder with solvent for reconstitution).

Mechanism of Action

Risperidone is a selective monoaminergic antagonist with a high affinity for:

- Serotonergic 5HT₂-receptors
- Dopaminergic D₂-receptors.

Risperidone also binds to:

- Alpha₁-adrenergic receptors

And with lower affinity, to:

- H₁-histaminergic receptors

- Alpha₂-adrenergic receptors.

Risperidone has no affinity for cholinergic receptors.

The antipsychotic activity of risperidone is considered to be attributable to both risperidone and its active metabolite 9-hydroxy-risperidone.

Central dopamine D₂-receptor antagonism is considered to be the prime mechanism of action by which conventional neuroleptics improve the positive symptoms of schizophrenia, but also induce extrapyramidal side effects and release of prolactin.

Pharmacodynamics

Risperidone is effective in the treatment of both the “**positive**” and “**negative**” symptoms of schizophrenia.

The symptoms of schizophrenia involve:

1 Positive symptoms:

- Delusions:
- Hallucinations:
- Formal thought disorder

2 Negative symptoms:

- Blunted affect (lack of emotional response)
- Apathy (loss of volition)
- Social withdrawal
- Paucity of speech

Pharmacokinetics

Absorption:

- Risperidone can be given orally or as an IM long acting depot preparation.

Risperidone is well absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours

Distribution:

- Risperidone is rapidly distributed. The volume of distribution is 1 to 2 L/kg.

- It is 88% bound to plasma albumin
- Risperidone can cross the human placenta
- Risperidone is excreted into human breast milk in small amounts.

Metabolism and excretion:

- Risperidone is partly metabolized by CYP2D6 to 9-hydroxyrisperidone, an active metabolite.
- Risperidone has an elimination half-life of about three hours in “extensive” metabolizers and 17 hours in “poor” metabolizers.

Clinical studies do not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

Indications

Indications for risperidone include:

1. Acute and chronic psychoses (e.g. schizophrenia)
2. Bipolar disorder
3. Behaviour disturbance in dementia.
4. Conduct and other disruptive behaviour disorders in people with subaverage intellectual functioning or mental retardation
5. Behavioural disorders in autism

Contraindications/ Precautions

These include:

1. Known hypersensitivity to risperidone (or paliperidone).
2. Caution with other CNS depressants, including alcohol, (synergistic sedation)
3. Caution with other agents of conditions that prolong the QT interval
4. Hypotension
5. Renal impairment
 - Dose should be reduced.

6. Parkinson's disease:

- Antipsychotics used in Parkinson's disease may aggravate the condition and may oppose the action of the dopamine agonists used to treat it.

Quetiapine or clozapine may be more suitable.

7. Hepatic

- Use with caution in severe hepatic impairment; consider dose reduction.

Pregnancy:

Risperidone is a category C drug with respect to pregnancy.

Category C drugs 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. These effects may be reversible. Specialised texts should be consulted for further details

From the limited information available, maternal use of risperidone has not been associated with an increased risk of birth defects or spontaneous abortions.

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

If risperidone is the medicine of choice, use at the lowest effective dose and monitor newborns for potential adverse effects such as self-limiting withdrawal symptoms. These symptoms include jitteriness, poor sucking reflex, tremor and restlessness.

Inform neonatal care providers of maternal use of risperidone as potential adverse effects or withdrawal symptoms may be present in newborns and require supportive treatments.

There is a lack of information about long term behavioural and cognitive outcomes among infants exposed in utero to risperidone.

Breastfeeding

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

Very small amounts of risperidone are excreted into breast milk.

Therefore, observe the breastfed infant for adverse effects such as excessive drowsiness, poor feeding and unusual sleeping pattern changes.

There is still a lack of information about the long term effects on developmental outcomes of children exposed to risperidone during breastfeeding.

Adverse Effects

1. Sedation
2. Orthostatic hypotension
3. Mild prolongation of QT_c interval
4. Extrapyramidal side effects:
 - As risperidone is a second generation antipsychotic, extrapyramidal effects are minimal compared to the older generation agents when used in usual therapeutic doses.

See Chlorpromazine for a description of these effects.

Note that however dystonias can be seen in high doses (> 4-6 mg) of risperidone and in cases of deliberate overdose

5. Neuroleptic malignant syndrome (NMS)
 - Again this is much less seen compared to the older generation of antipsychotic agents.

Dosing

Oral:

For acute behavioural disturbances:

- Risperidone **0.5 - 1 mg orally**, repeated **every 2 - 4 hours**, titrated to clinical response, up to a maximum of **6 mg in 24 hours** ¹

IM Depot Administration: ²

Long-acting IM under the direction of a specialist psychiatrist:

Adults:

- 25 mg every 2 weeks; increase if necessary to maximum of 37.5 - 50 mg every 2 weeks.

Give supplemental oral antipsychotic for the first 3 weeks.

Do not adjust the dose more frequently than every 4 weeks.

Full effects of a dose increase will not be seen for around 3 weeks.



"Jockeys at the Racecourse", oil on canvas, c. 1872, Edgar Degas.

References

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