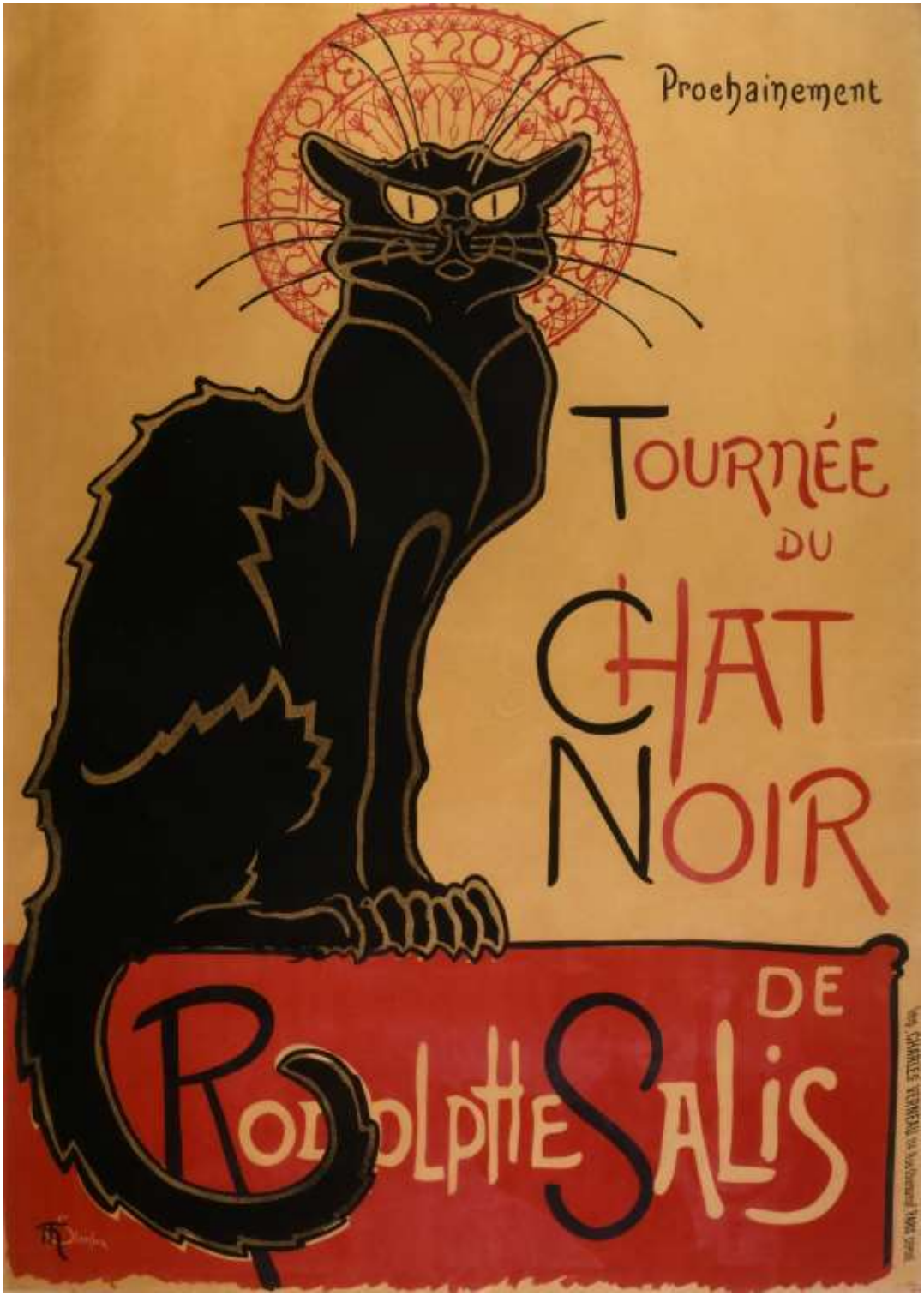
THE NORTHERN HOSPITAL

VALPROATE SODIUM



"Le Chat Noir", (The Black Cat), poster, Paris 1881, Theophile Steinlen.

When the struggling young painter Rodolphe Salis opened Le Chat Noir in 1881, he had no idea he was about to make history. After all, his nightspot was a scruffy place, located at the bottom of the Butte, at 84 Boulevard de Rochechouart (18th). Even in those days, this was not a good address, but Salis' collaborator, the poet Emile Goudeau, helped spread the word. Soon poets, musicians and artists began to congregate there, in a decor that featured threadbare tapestries, stained glass and a throne-like Louis XIII chair. Comfortably ensconced in this mock-medieval setting, the Chat Noir regulars readily discussed their work, gave readings sang songs, and skewered the Establishment. It quickly became a kind of club, the headquarters for a talented avant-garde who enjoyed sharing ideas as well as drinks and bonhomie with one another. In this zesty atmosphere, modern cabaret was born.

Despite the cabaret's location in the heart of the Pigalle quarter and its poster image (created by Theophile Steinlen) of a lecherous looking tomcat parched on a wall, this was not some sort of bordello experience. Le Chat Noir's clientele were looking for good times, to be sure, but their idea of a good time was a convivial (and well lubricated) evening based on shared intellectual and cultural interests. Salis himself described the place as an "artistic cabaret" and many of Salis' regulars came from a Left Bank literary group, the Hydropathes, which Goudeau had earlier founded with the intent of making young writers and poets like himself better known through public readings in cafes. When Salis set up the Chat Noir cabaret, Goudeau simply moved his group to the new quarters.

The result was a happy combination of serious poetry and inspired flippancy, with both entertainment and publicity in mind. Le Chat Noir published its own literary newspaper, which Goudeau edited, and promoted the work of its contributors. Before long, the place was jammed with poets, painters and musicians, including the composer Erik Satie, who briefly played the cabaret's piano, and Claude Debussy, who occasionally played as well. Other regulars included the poets Stephane Mallarme and Paul Verlaine.

In 1885, business was good enough that Salis could afford to move to larger quarters at a better address, at 12 Rue de Laval (now Rue Victor-Masse). He sold the old location, to the rakish chansonnier Aristide Bruant, who opened his own cabaret there., calling it the Mirliton. Bruant,, whom Toulouse-Lautrec immortalized in his wide-brimmed black hat and crimson scarf, specialized in social protest and the comedy of insult. He redecorated Salis' former space with old warming pans, chamber pots, and the Chat Noir's forgotten Louis XIII chair (which he irreverently suspended from the ceiling) and soon found his clientele amoung the bourgeoisie, out for some rough humour and a good time.

The Mirliton thrived, but the Chat Noir regulars found the atmosphere at their now location a bit stiff and formal for their liking and they began to drift away. In response Salis started up a pantomime shadow theatre, which soon became wildly popular among the avant-garde. Henri Riviere, a young illustrator and designer, was the originator and producer of this simple but effective form of theatre, which used zinc a cut-outs of back lit figures that appeared as silhouettes as they moved back and forth on runners positioned at different distances behind a white fabric screen. Caran d'Ache and several other artists , as well as a coterie of journalists and writers, joined Riviere in creating the many sketches and designing the figures, sets, and program covers. Together they created more

than forty plays, often on Biblical, and historical themes, with hundreds of cleverly designed silhouettes, including those of current notables - such as an amusingly bear-like Zola and Salis himself.

Of obvious artistic and literary merit, in addition to being good fun this shadow theatre continued to be a draw for more than a decade, until Salis' death. Look for any remains, and all you will find is a plaque on the wall telling passersby that this edifice, once the home of the famous cabaret Le Chat Noir, "was consecrated to the muses and to joy".

Mary McAuliffe, "Dawn of the Belle Epoch", 2011.

Rodolphe Salis made Le Chat Noir a very great success! For f our years it attracted the very best of the Parisian avant-garde, in writers, musicians, and artists. Much of its appeal lay in its informal and jovial atmosphere. It was so successful, that Rodolphe decided he could move a little more "upmarket" and in 1881, he moved Le Chat Noir to a better address - 12 Rue de Laval. However much to his surprise, he began to lose much of his old regular clientele - Le Chat Noir was just not the same! - a little too elegant, fashionable - ostentatious even! Perhaps Rodolphe has badly miscalculated. But he was genius when it came to business, it was clear that he would have to reinvent Le Chat - and that is precisely what he did! He started up quirky a pantomime shadow theatre, and in one time at all, Le Chat Noir was once again the "a la mode" of all of Paris!

Sodium valproate was once all the rage in the treatment of epilepsy - then a veritable barrage of new agents challenged its supremacy. Big Pharma decided a "reinvention" was in order "a la", Le Chat Noir! New indications - resurgence of popularity - Viola! Once again sodium valproate is "al la mode"!

Shadow Puppets of Le Chat Noir, 1894, Musee D'Orsay. Created by Henri Riviere and Jules Depaquit. The "bear-like" Emile Zola appears top right.

VALPROATE SODIUM

Introduction

Valproate (or **sodium valproate** or **valproic acid**), (trade name in Australia, "**Epilim**") is a broad spectrum anticonvulsant drug used to treat either generalized or focal seizures.

More recently its indications for use have increased and it is now also prescribed for:

- **Status epilepticus**
- Mania and Bipolar disorder
- Migraine prophylaxis.
- Neuropathic pain

Valproate has been prescribed widely for **epilepsy** for many decades.

Given that *new indications* for its use continue to emerge, it is increasingly important for ED clinicians to remain cognisant of the drug's adverse effects.

It is potentially lethal if taken in acute deliberate overdose.

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

History

Sodium valproate was first marketed as an anticonvulsant almost 50 years ago in France.

Today it is the most prescribed antiepileptic drug worldwide

In more recent years a number of new indications for its use have been found.

Chemistry

Sodium valproate is sodium propylacetic acid.

It is quite dissimilar to many other established anticonvulsants drugs such as barbiturates, hydantoins, succinamides, oxazolidinediones and acetylureas in that it has no nitrogen or aromatic moiety.

Classification

There is no general consensus on the classification of anticonvulsant drugs, in part due to the wide structural variation as well as the wide variation in the mechanisms of actions of these agents.

The precise mechanisms of action of the non-barbiturate and non-benzodiazepines agents are imperfectly understood.

Many agents probably have more than one action, and individual specific actions can overlap between agents.

In the broadest terms modern anticonvulsant agents can be divided into the barbiturates, the benzodiazepines and other agents.

1. Barbiturates:

   The principally used agents are:

   - Phenobarbitone
   - Primidone

2. Benzodiazepines:

   The principally used agents are:

   - Diazepam
   - Midazolam
   - Clonazepam

3. Other antiepileptics:

   These agents include:

   - Carbamazepine
   - Ethosuximide
   - Gabapentin
   - Lacosamide
   - Lamotrigine
   - Levetiracetam
   - Oxcarbazepine
   - Phenytoin
   - Perampanel
   - Pregabalin
   - Sulthiame
   - Tiagabine
   - Topiramate
   - **Valproate**
   - Vigabatrin
   - Zonisamide

Preparations

Valproate as **Sodium valproate**:

Tablets:

- 100 mg, 200 mg, 500 mg.

  Both **immediate-release** and **enteric coated extended release** preparations are available.

Liquid:

- 40 mg/mL, 300 mL

Ampoules:

- 400 mg as powder with solvent.

Mechanism of Action

Valproate's mode of action of action has not been fully established.

A number of theories exist including:

1. Blockade of voltage dependent Na^+ channels

2. Increased brain levels of gamma-aminobutyric acid (**GABA**).

   - The GABA-ergic effect is also believed to possibly contribute towards the anti-manic properties of sodium valproate.

     In animal models, valproate raises cerebral and cerebellar levels of the inhibitory synaptic transmitter, GABA, possibly by inhibiting GABA degradative enzymes, such as GABA transaminase and/or succinic semialdehyde dehydrogenase and/or by inhibiting the reuptake of GABA by neuronal cells. [3]

3. **Reduced** release of *excitatory* amino acid neurotransmitters. [4]

Pharmacodynamics

Sodium valproate has been shown to be effective in the treatment of absence seizures (petit mal), tonic-clonic seizures (grand mal), myoclonic seizures, and in those with partial (focal) seizures.

Sodium valproate appears to have **less sedative** effect than other antiepileptic drugs. [3]

In one study valproate has been shown to be significantly more effective than placebo in the treatment of acute mania and has been reported to be comparable to lithium. [3]

Pharmacokinetics

Absorption

- Valproate can be given **orally** or **IV.**

  It should **not** be given IM because of the potential for tissue necrosis.

  Valproate is absorbed well and rapidly from the GI tract.

  When administered orally sodium valproate has almost complete bioavailability

- When fasting, oral valproate reaches peak plasma concentrations within **4 hours** for immediate-release formulations and within **7 hours** for enteric coated formulations.

- Drugs that slow the GI tract (such as opiates, antihistamines) may delay absorption of valproate during co-ingestion.

Distribution

- The volume of distribution is small at 0.1- 0.2 L/ kg

- Valproate is highly protein bound 90%, (60% to albumin).

- Valproate can cross the human placenta.

- Valproate is distributed into human breast milk in small amounts only.

Metabolism and elimination

- Valproate is almost completely metabolized in the liver, mainly by glucuronidation.

  It then undergoes further metabolism with oxidation, which is complex and involves several cytochrome P450 enzyme systems.

  It has multiple metabolites which may contribute to both its efficacy and toxicity.

  There are many potential drug interactions.

- The half-life is long at 8 - 20 hours, but may be much longer in some situations such as renal impairment or overdose.

Indications

These include: [2]

Seizure activity:

1. Primary generalized epilepsy, including:
    - Tonic-clonic
    - Myoclonic
    - Atonic seizures
    - Absence
2. Simple and complex partial (focal) seizures

More recent indications have included:

3. Bipolar disorder
4. Prevention of migraine, when other treatments have failed
5. Neuropathic pain:
    - This indication is controversial but some physicians use it for cases of neuropathic pain where other proven treatment options have failed, are not available, or are not tolerated. [4]

Contra-indications/precautions

These include:

1. Known allergy to valproate
2. Women of child-bearing age:
    - Avoid if possible in women of child bearing age using inadequate contraception, due to teratogenic risk.

      If there is no effective alternative, use lowest possible dose.

      See also below.
3. Children:

- Not recommended in children because of the relatively high risk of hepatitis and pancreatitis.

4. Liver impairment.

5. Pancreatic dysfunction (contraindicated).

6. Porphyria (contraindicated).

7. Drug interactions:

   - There are many potential drug interactions which can increase or decrease the effects of valproate - specialist texts should be consulted.

8. Urea cycle disorders (contraindicated):

   - Hyperammonaemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders, a group of rare genetic abnormalities, particularly ornithine transcarbamylase deficiency.

Pregnancy

Valproate is a category D drug with respect to pregnancy.

Category D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

Maternal use of valproate, both as monotherapy and as part of a polytherapy regimen, has been associated with an increased risk of congenital malformations.

“Fetal valproate syndrome” refers to a consistent craniofacial phenotype, often with major malformations, growth deficiency or neurodevelopmental dysfunction. Other congenital malformations associated with exposure to valproate include neural tube defects (NTD), cardiac defects, skeletal or limb defects, skin or muscle defects, and urogenital defects (e.g. hypospadias in about 50% of males). Several studies have suggested that the risk for major congenital malformations is dose dependent, with risks increasing with dose greater than or equal to 1000 mg daily.

When valproate treatment during pregnancy cannot be avoided, use the lowest effective dose to minimize teratogenic risk. Appropriate ultrasonographic and other examinations, such as measuring maternal serum levels of alpha-fetoprotein and fetal cardiography, should be offered to women using valproate during pregnancy.

Valproate is known to interfere with folate metabolism. Taking folic acid supplementation in early pregnancy has been found to reduce the chance for giving birth

to a child with neural tube defects. Although there is no evidence to show higher doses of folic acid supplementation is better than the standard dose (400 micrograms), there are no known harmful effects on the development of the baby from taking higher doses during pregnancy. A small study has found that taking folic acid supplementation throughout pregnancy may improve psychological and social development in children. It is recommended to take higher dose folic acid supplementation (1 to 5mg daily) whilst trying to conceive and during the first trimester of pregnancy and continue with at least 400 microgram daily in the second and third trimesters.

Infants of women with epilepsy taking antiepileptic medicines may have an increased risk of growth restriction, small for gestational age, transiently reduced Apgar score and low birth weight. Valproate is approximately 90% protein bound and cleared through hepatic metabolism. Pregnancy may affect the disposition of valproate, especially in late pregnancy. When valproate is the treatment of choice during pregnancy, valproate plasma levels may be monitored and titrated to the lowest effective dose.

Infants exposed to valproate in utero may develop neurological manifestations, including irritability, jitteriness, hypotonia, hypertonia (or variable tone) and feeding problems. These signs and symptoms usually occur within 12 to 48 hours after birth. Other possible neonatal complications include hepatic toxicity and hypoglycaemia.

Several studies have suggested that children exposed to valproate in utero show poorer cognitive outcomes compared to infants exposed to other antiepileptic medicines. Maternal use of valproate has also been associated with an increased risk of autism spectrum disorder and childhood autism. Further investigations are needed to confirm these findings.

Breast feeding:

Although valproate probably does not enter breast milk in clinically important amounts, the drug's manufacturers advise *against* breastfeeding.

Women with epilepsy who are currently pregnant or who have given birth recently are encouraged to contact the Australian Pregnancy Register at: [4]

- www.neuroscience.org.au/apr

Or

- 1800 069 722.

Small amounts of valproate are excreted to breast milk, but these amounts are unlikely to cause serious adverse effects in breastfed infants.

However, a single case of thrombocytopenic purpura, anaemia and reticulocytosis in an infant exposed to valproate via breast milk has been reported, but these symptoms resolved upon cessation of breastfeeding.

If a breastfed infant shows signs of adverse effects, consider monitoring the infant's liver and platelet function.

No significant difference in intelligence quotient (IQ) has been found at 6 years of age between infants who were breastfed and those who were not breastfed by mothers taking valproate, consistent with another study at age 3 years. A study has found that breastfeeding in women using antiepileptic medicines was not associated with any harmful effects on child development at 6 to 36 months of age, and it protected against low weight during the postnatal period. Further investigations are needed to confirm these findings.

Adverse Effects

These include:

1. Allergic reactions
2. CNS:
    - Mild sedation:
        - ♥ Valproic acid may potentiate the CNS depressant activity of alcohol.
    - Ataxia
3. *Transient* nausea or dizziness may occur shortly after **IV injection.** [2]
4. GIT upset:

    Gastrointestinal adverse effects are common, particularly at the start of therapy.

    These can include:

    - GIT upset:
        - ♥ Nausea, abdominal cramps, diarrhoea.
    - Pancreatitis:
        - ♥ Potentially severe/ fatal.
    - Liver impairment:

        Elevated aminotransferase concentrations occur that are dose-related. Reactions ne be potentially severe/ fatal.

Although *liver function tests* may alter during treatment they are, in themselves, not reliable in predicting which patients will develop frank liver failure.

The risk of valproate-induced hepatic failure is increased in: [2]

- ♥ Children, especially if < 3 years.
- ♥ Patients with congenital metabolic or degenerative disorders
- ♥ Patients with seizure disorders and mental retardation
- ♥ Patients with organic brain disease
- ♥ Patients taking multiple antiepileptic drugs
- ♥ Patients with a family history of hepatic disease
- ♥ Patients starting valproate within 3 months of liver disease
- ♥ Patients with certain mutations in the POLG gene.

5. Hematological disturbances:

- Thrombocytopenia, anaemia, leucopenia.

6. Dermatological:

These reactions may include:

- Pruritus/ urticaria
- Erythema multiforme

Or more seriously:

- Stevens- Johnson syndrome
- Toxic epidermal necrolysis
- DRESS.

Valproate is potentially lethal in acute intentional overdose.

See separate document on Valproate Overdose (in Toxicology folder).

Dosing

Epilepsy:

Routine prophylactic:

In general terms for Adults:

- Initially, 600 mg orally daily in 2 doses; increase every 3 days by 200 mg daily according to response.

  Maximum daily dose is **2.5 grams daily.**

  If withdrawal of valproate is required, this should be done slowly if possible. Rapid cessation may provoke seizures in patients with epilepsy.

Refractory seizure activity/ status epilepticus:

- There is some evidence that **IV** sodium valproate may be more effective than IV phenytoin.

  The Neurology Therapeutic Guidelines recommends the following dosing regimen for situations of **status epilepticus**: [1]

  - **Sodium valproate 40 mg/kg - up to 3000 mg intravenously over 3 - 5 minutes**.

Bipolar Disorder

There is strong evidence to support a linear relationship between serum drug concentration and therapeutic response in **acute mania** for sodium valproate. [1]

Particular benefit has been demonstrated for concentrations above 660 micromol/L (94 mg/L). Toxicity is likely at concentrations of 875 micromol/L (125 mg/L) or higher. [1]

For treatment and prophylaxis:

- Sodium valproate 200 - 400 mg orally, twice daily.

  The dose should be increased weekly in increments of 200 - 400 mg per day and the serum concentration determined after 3 days of steady-dose treatment.

  Most patients require a daily dose of 1500 to 3000 mg to obtain a therapeutic serum concentration

Migraine prophylaxis:

Adults: 200 - 400 mg orally twice daily. [2]

References

1. eTG - July 2019.

2. Valproate in Australian Medicines Handbook Website Accessed July 2015

3 Valproate in MIMs Website 1 June 2014.

4. Ahamed Zawab and John Carmody, Safe use of sodium valproate. Aust Prescr 2014; 37:124-7.

5. Valproate in RWH Pregnancy & Breastfeeding Guidelines, 1 November 2018.

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