# Valproic Acid-Induced Hyperammonemia: Systematic Review

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## Background

- Hyperammonemia is a documented adverse effect of valproic acid (VPA)[1]
- Its clinical significance and incidence is unclear[1,2]
- Its risk factors and its association with VPA levels are not well defined[3]
- There is no clear guidance regarding the type of monitoring or intervention required[1-3]
- This systematic review aims to summarize evidence available about VPA-induced hyperammonemia and its clinical outcomes and management

## Clinical Questions

1. What is the **incidence** of hyperammonemia?
2. How are **valproic acid levels** associated with hyperammonemia?
3. What are the **risk factors**?
4. What are the **consequences**?
5. What are the most effective **treatments**?
6. What are the most appropriate **monitoring parameters**?
7. Should **ammonia levels be routinely drawn** in the absence of symptoms?

## Methods

| | |
|---|---|
| Search terms | valproic acid, valproate, valproic, VPA, depakene, depacon, depakote, divalproex, epival, dipropylacetic, 2-propylvaleric, hyperammonemia, ammonia, and NH3 |
| Databases | Medline, Embase, PsycINFO, Web of Science |
| Date | Up till Sep 14th, 2020 |
| Titles and abstracts screening and full texts reviewing | Two independent reviewers. A third reviewer resolved conflicting results |
| Data extraction | A single reviewer. A second reviewer conducted a random audit of 10% of the included articles |
| Inclusion Criteria | Hyperammonemia in patients, regardless of gender and age, treated with VPA for any condition at any clinical setting |
| Exclusion Criteria | Pharmacokinetic studies. One time overdose of VPA |

## Figure 1. PRISMA Flow Diagram for Systematic Review



- MEDLINE 1946 to 2020 — 515 citations
- EMBASE 1946 to 2020 — 1221 citations
- Web of Science 1990 to 2020 — 491 citations
- PsycINFO 1992 to 2021 — 105 citations
- 1624 non-duplicate citations screened
- Inclusion/exclusion criteria applied → 876 articles excluded after failing to meet the inclusion criteria in title/abstract screening
- 582 articles retrieved → 10 articles cannot be found
- Inclusion/exclusion criteria applied → 339 articles excluded after full text screening: 37 reviews, 2 pharmacokinetic related, 38 VPA overdose related, 175 met exclusion criteria
- 232 articles included: 2 randomized controlled trials, 72 cohort studies, 32 prospective (17 adult, 12 pediatrics), 38 retrospective (22 adult, 16 pediatric), 2 cross sectional (1 adult, 1 pediatric), 153 case studies (145 adults, 46 pediatric), 5 case series

## Table 1. Results – Incidence and Associated VPA Level

| | RCT** | Prospective Cohort | | Retrospective Cohort | | Cross Sectional |
|---|---|---|---|---|---|---|
| | Pediatrics | Adults | Pediatrics | Adults | Pediatrics | Pediatrics |
| Symptomatic hyperammonemia incidence (%) | 1 | 0.7 – 10 | 6.6 | 3.5 – 36 | 1 – 22.2 | |
| Asymptomatic hyperammonemia incidence (%) | 4 | 7.7 – 20 | 14.3 – 22.7 | 7.7 – 43.2 | 2.43 – 73 | 41.3 |
| Unspecified hyperammonemia incidence (%) | | 28 – 55.3 | | 19 – 77 | 9.9 – 47.6 | |
| VPA level for symptomatic hyperammonemia (umol/L) | | 418 – 839 | | 647.94 – 839 | | |
| VPA level for asymptomatic hyperammonemia (umol/L) | | | | 311.35 | 376 – 586 | |

*Greyed area = no available data
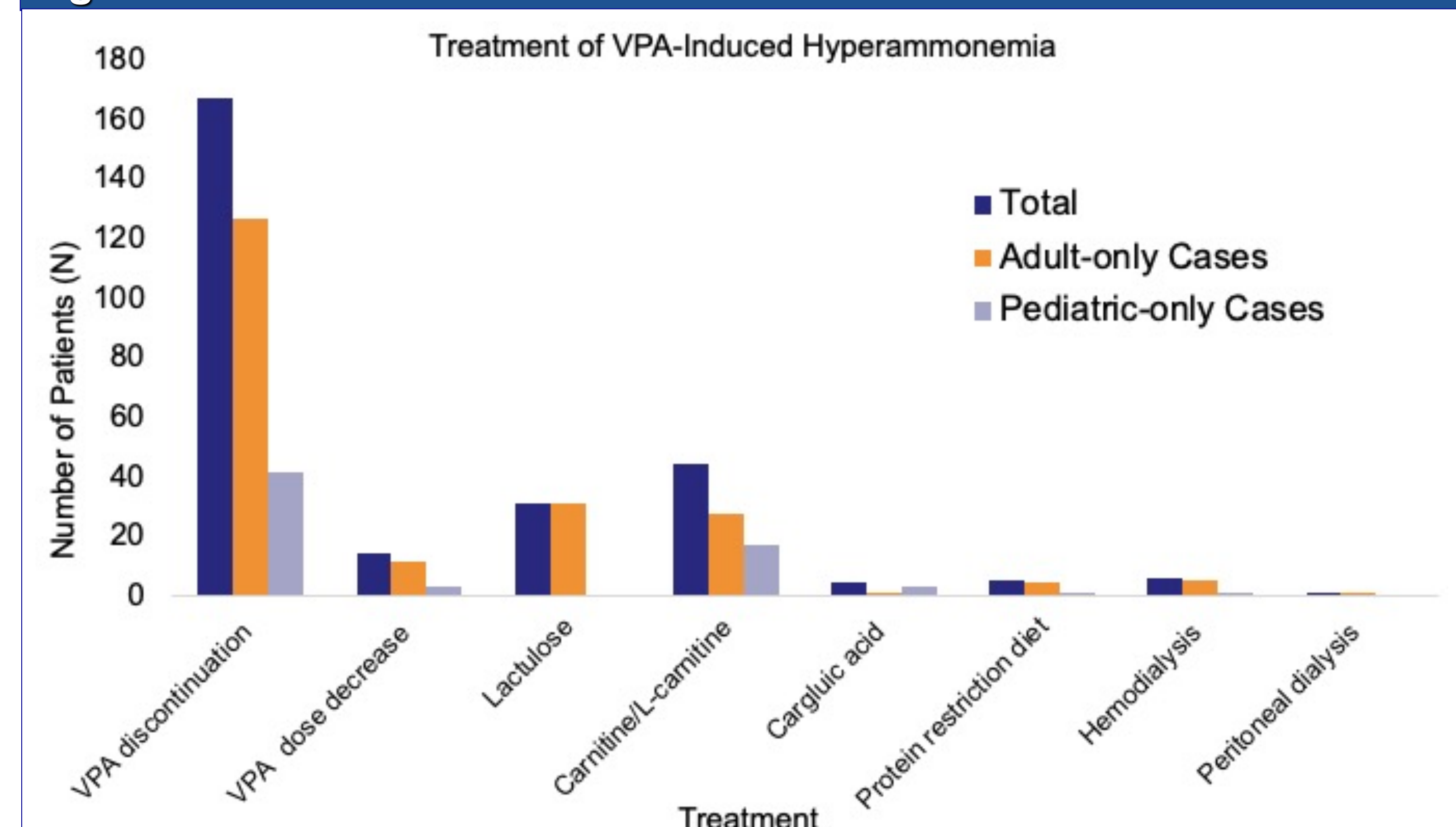
** RCT = randomized controlled trial

## Table 2. Results – Risk Factors

| | Prospective Cohort | | Retrospective Cohort | | Cross Sectional |
|---|---|---|---|---|---|
| | Adults | Pediatrics | Adults | Pediatrics | Pediatrics |
| Risk factors identified and its correlation | **Antiepileptic Use**<br>• Phenobarbital use (OR 4.50; 95% CI 1.04-19.34)<br>• Phenytoin use (OR 1.87; 95% CI 1.01-3.45)<br>**Mood Stabilizer Use**<br>• Concurrent mood stabilizer use (F=4.66, p=0.04)<br>**Antipsychotic Use**<br>• Blonanserin use (F=7.8, p<0.01)<br>• Risperidone use (F=5.17, p= 0.03)<br>**VPA-related parameters**<br>• Total daily dose (r=0.216, p=0.036)<br>• VPA blood level (r=0.207, p=0.0045)<br>**Patient specific factors**<br>• Total number of medications concurrently used (r=0.213, p=0.039)<br>• Aneurysmal subarachnoid hemorrhage (OR 1.91; 95% CI 1.06-3.46)<br>**Amino Acid**<br>• Glutamate level (r=0.44, p<0.01)<br>• Tryptophan level (r=0.35, p=0.03)<br>• Citrulline level (r=-0.42, p=0.01)<br>• Glutamine level (r=-0.54, p<0.01)<br>• Glycine level (r=-0.54, p<0.01) | **Transaminases**<br>• Serum glutamic pyruvic transaminase level (r=0.530, p<0.01)<br>• Serum glutamic oxaloacetate transaminase level (r=0.435, p<0.05)<br>**Carnitine**<br>• Free carnitine level (r=-0.67, p<0.0001); (r=-0.935, p<0.0001)<br>• Total carnitine level (r=-0.896, p<0.0001)<br>**Patient specific factors**<br>• Age (r=-0.532, p<0.01) | **VPA-related parameters**<br>• Serum VPA level (r=0.149, p<0.05); (r=0.522, p=0.004)<br>• VPA starting dose (r=0.472, p=0.011)<br>• VPA dose >20 mg/kg/day (OR 4.1; 95% CI 1.6 - 10.8)<br>**Carnitine**<br>• Acylcarnitine level (r=-0.183, p<0.05)<br>**Patient specific factors**<br>• Age (r=0.367, p<0.001)<br>• Use of mechanical ventilation (OR 5.65, p=0.037) | **VPA-related parameters**<br>• Serum total VPA level (r=0.55, p=0.00086); (r=0.57, p<0.01)<br>**Patient specific factors**<br>• Liver injury (OR 4.60; 95% CI 1.27-16.74; p=0.021)<br>• Age (OR 0.97 95% CI 0.94-0.9)<br>**Antiepileptic Use**<br>• Concurrent topiramate use (OR 2.69 95% CI 1.78-4.05)<br>• Concurrent zonisamide use (OR 1.72 95% CI 1.33-2.23) | **VPA-related parameters**<br>• VPA serum level (r=0.82, p<0.001)<br>• VPA dose (r=0.78, p<0.001) |

## Results – Consequences

- Reported consequences of VPA-induced hyperammonemia were encephalopathy, confusion, seizure, somnolence, disorientation, vomiting, nausea, decreased psychomotor response, and aggression
- The most common consequence of hyperammonemia reported in adult case reports was confusion (N=39/145; 26.9%) while in pediatric case reports was vomiting (N=12/46; 26.1%)

## Figure 3. Results – Treatments



Treatment of VPA-Induced Hyperammonemia (Total, Adult-only Cases, Pediatric-only Cases; Number of Patients (N) vs Treatment: VPA discontinuation, VPA dose decrease, Lactulose, Carnitine/L-carnitine, Carglulic acid, Protein restriction diet, Hemodialysis, Peritoneal dialysis)

- All patients improved clinically after intervention implemented except one, who died from Steven Johnson Syndrome

## Limitations

- Variability in the definitions of hyperammonemia in between studies
- Heterogeneity of studies did not allow data to be pooled
- Patients with liver dysfunction were often excluded
- Included studies could not determine the benefit of routine ammonia level monitoring for improving clinical outcomes

## Clinical Takeaways

- Asymptomatic hyperammonemia incidence was higher than symptomatic hyperammonemia. Both were commonly reported within the therapeutic range of VPA
- Concomitant mood stabilizer, antipsychotic and antiepileptic use and abnormal amino acid metabolism were some risk factors identified for hyperammonemia
- Most patients improved clinically after intervention implemented, such as VPA discontinuation
- Monitoring for VPA-induced hyperammonemia should be based on symptoms instead of VPA level or ammonia level. It is unclear whether there is a benefit in monitoring ammonia levels in the absence of symptoms. Further research is required
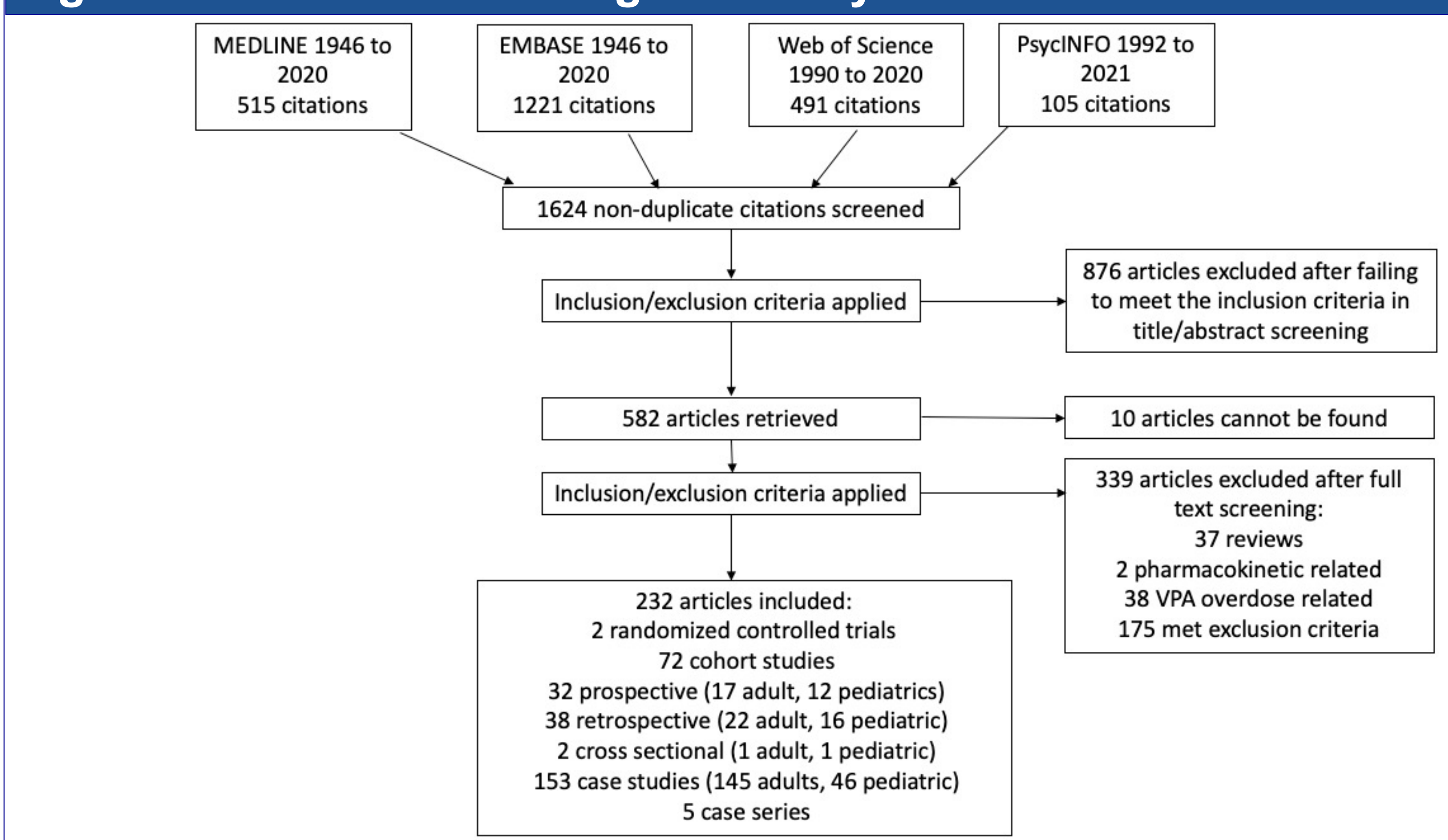
## References
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