Episode 071: Valproic Acid: History, Mechanism, Treatment in Bipolar, Schizophrenia, Aggression and Side Effects with Dr. Cummings

Alex Ramos B.A., David Puder, M.D., Michael Cummings, M.D.

DAVID PUDER, M.D.
PSYCHIATRY & PSYCHOTHERAPY

This PDF is a supplement to the podcast "Psychiatry & Psychotherapy" found on **iTunes**, **Google Play**, **Stitcher**, **Overcast**, **PlayerFM**, **PodBean**, **TuneIn**, **Podtail**, **Blubrry**, **Podfanatic**

There are no conflicts of interest for this episode.

We had an episode on Valproic Acid with Dr. Cummings…

History:

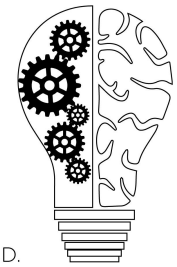
- Valproic Acid is an 8 carbon branch carboxylic acid (formerly named 2-propylvaleric Acid). It is derived from valeric acid which is a compound derived from Valerian Root (herbal product that is sometimes used for anxiety and sedation).
- Originally synthesized in 1882 by BS Burton, not as a medication but intended to be an inactive solvent for use in medical research. It was used as a solvent until 1962 when research was being done where researchers were attempting to give animals compounds in order to induce seizures. They found that compounds that had been dissolved in valproic acid did not induce seizures which led them to the realization of its anticonvulsant properties. It was officially approved as an antiepileptic in 1972 in France.
- In 1982, researchers, e.g. Robert Post (NIMH), began to look at anticonvulsants to determine if they had any mood stabilizing effects by inhibiting limbic kindling.
- They found that valproate is a mood stabilizer that is effective toward the manic pole of bipolar disorder more than the depressed pole and also provides good prophylaxis (lengthens the time between mood episodes).

Mechanism of Action (Perucca, 2002)

- While its exact mechanism of action is still unclear, in the broad sense valproic acid dampens the excitability of the limbic portion of the nervous system. There is evidence that valproate increases **GABA synthesis and release in certain brain regions**. It has also been found to decrease the release of excitatory amino acid **beta hydroxybutyric acid** and to reduce neuronal excitation by activation of **NMDA receptors**. Valproate also acts directly on excitatory membranes by **blocking voltage gated sodium channels**. Valproic acid is also thought to alter the concentration of guanine synthase kinase (regulates cell excitability) and activity of protein kinase C (alters excitability of neurons).
- It's efficacy in treating some psychiatric disorders is also thought to come from valproate having some capacity to modulate dopamine and serotonin transmission.

Episode 071: Valproic Acid: History, Mechanism, Treatment in Bipolar, Schizophrenia, Aggression and Side Effects with Dr. Cummings

Alex Ramos B.A., David Puder, M.D., Michael Cummings, M.D.

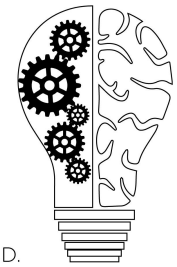


Therapeutic Blood levels

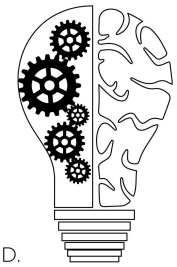
- It is important to note that the effective concentrations for patients being treated for epilepsy or for psychiatric reasons differ.
- For seizures: 50-100 mcg/mL
- Mood disorders/impulsivity/TBI/personality disorder or any psychiatric condition require a higher concentration in order to be effective: 80-120 mcg/mL. Anything below that is most likely not doing much for the patient because the drug is highly protein bound.

What it is used for

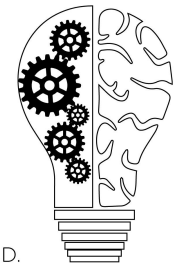
- Bipolar Disorder
    - Bipolar disorder (BD) is a mental disorder covered in prior episodes. Treatment for this disorder includes using mood stabilizers and antipsychotics. Valproate has traditionally been used to treat acute manic episodes in patients with BD.
    - A systematic review (Jochim, 2019) was performed to assess the efficacy of valproate for acute manic episodes in BD compared to placebo, other pharmacologic treatments or a combination of pharmacologic treatments in the adult, pediatric, and adolescent population. The primary outcome used to assess for efficacy was response rate.
    - This review found that valproate is an efficacious treatment for acute mania in adults compared to placebo (45% vs 29%, OR 2.05, 95% CI 1.32 to 3.20; 4 studies, 869 participants). When comparing valproate to lithium they found that there was little to no difference in response rate (56% vs 62%, OR 0.80, 95% CI 0.48 to 1.35; 3 studies, 356 participants). They also found little to no difference in response rate between valproate and olanzapine (38% vs 44%, OR 0.77, 95% CI 0.48 to 1.25; 2 studies, 667 participants).
    - Dr. Cummings explains that the differences between these medications seem to come from their prophylactic effects. **Valproic acid and Lithium both appear to have a longer survival curve between mood episodes (longer length of time before another mood episode occurs) when compared to olanzapine or other second generation antipsychotics** that are indicated for mood stabilization. Lithium has the broadest range of efficacy, it is effective for hypomania, mania and is also somewhat antidepressant. On the other hand, valproic acid is as effective as lithium in regard to acute mania, or hypomanic symptoms but shows less efficacy when it comes to bipolar depression.
        - How to choose between these medications:
            - If a patient has previously had a positive past response to valproic acid then it would be favored



        - If a patient cannot tolerate lithium (i.e if they have some form of renal impairment) then valproic acid would be favored
        - If a patient is intolerant to Lithium or valproic acid or has shown no response to both, Olanzapine would become the drug of choice.
        - If a patient is reluctant to take oral medications, Olanzapine is available in an injectable form making it a more favorable choice for these patients.
    - Loading dose for acute mania
        - A common error that occurs with valproic acid is that it is started at a low dose. At concentrations of less than 50 mcg/mL almost all of it is bound to albumin and not much may happen because there is not enough to enter the brain (only the free form is active). In acute mania, the typical loading dose for valproic acid is 20-30 mg/kg per day, divided into 2 doses.
- Schizophrenia
    - Valproic acid seems to be useful for agitation in patients in an acute psychotic exacerbation. Valproic acid has a rapid onset and is good at calming that agitation while waiting for the antipsychotics (slow onset) to work on the underlying psychotic symptoms.
    - Once antipsychotics become effective, **in a schizophrenic patient who has no elements of bipolar disorder valproic acid does not seem to add anything to their treatment**. However, **if they do have some elements of bipolar diathesis these patients may benefit from ongoing treatment with valproic acid**.
    - Valproate for schizophrenia (Wang, 2016)
        - While the primary medication for patients with schizophrenia is an antipsychotic, there are still a minority of patients (at least 30%) who continue to have symptoms. A number of adjunctive treatments have been tried in addition to antipsychotics in order to try to reduce these symptoms including valproate.
        - Studies that were comparing the effects or treating patients with valproate + an antipsychotic versus antipsychotics + placebo or antipsychotics alone were compared in patients with schizophrenia. They found that adding valproate to antipsychotic treatment had a more effective response to patients mental state than adding placebo to an antipsychotic drug or taking an antipsychotic alone. Specifically, **valproate was found to help with the symptoms of excitement and aggression in this patient population**.



    - Divalproex ER combined with Olanzapine or Risperidone for treatment of acute exacerbations of schizophrenia (Casey, 2008)
        - A study of 402 patients who were hospitalized with an acute exacerbation of schizophrenia were randomized and treated over 12 weeks with the objective to see the efficacy and safety of divalproex versus placebo in combination with risperidone or olanzapine.
        - 103 received olanzapine/placebo, 99 received olanzapine/divalproex, 101 received risperidone/placebo, and 99 received risperidone/divalproex.
        - Study found that there was no difference in the PANSS total score (scale used to measure symptom severity in patients with schizophrenia based on their positive or negative symptoms) between the combination group or monotherapy group ($p = 0.307$).
        - Found that there was no significant difference in the PANSS positive subscale at day 14 ($p = 0.473$) or day 84 ($p = 0.623$). However, on the PANSS negative subscale antipsychotic monotherapy showed greater benefit over combo therapy ($p = 0.085$).
- Borderline Personality Disorder (BPD)
    - BPD falls under cluster B personality disorders. It is a serious mental disorder characterized by a pattern of instability in affect regulation, impulse control, interpersonal relationships and self-image (Lieb, 2004). Affective instability, impulsivity and aggression are distinctive characteristics and often targets for treatment.
    - While pharmacotherapy is not the mainstay of treatment for BPD. Dr. Cummings describes an approach of choosing certain target symptoms that are impairing a person's ability the most and targeting them with therapeutic amounts of a chosen medication instead of using multiple medications (which is often seen in these patients).
    - Valproate for BPD (Hollander, 2005)
        - 52 patients with BPD were randomly assigned to treatment with divalproex or placebo for 12 weeks. Median baseline aggression score on the Overt Aggression Scale was 33.5 (mean = 53.5) in the divalproex group and 35.2 (mean = 52.8) in the placebo group. Efficacy was measured by a change in the overt aggression scale over treatment time.
        - Patients who were treated with divalproex were shown to have the greatest reduction in impulsive aggression than those treated with placebo. Study concluded that divalproex is a favorable treatment choice for the symptoms of impulsive behavior in BPD.
- Anger/Aggression



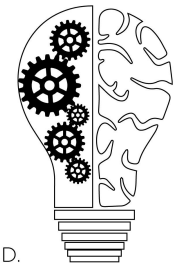
    - Predatory
        - There is currently no good evidence that valproic acid is effective for this
    - Impulsive
        - Impulsivity or impulsive violence is a result of a lack of adequate top down inhibition of the limbic system. The prefrontal cortex is responsible for evaluating the potential consequences of our impulses. For example, if someone has an impulsive thought their prefrontal cortex tells buts a brake on it. This seems to be inadequate in some patients with Traumatic Brain Injury or who have Schizophrenia or suffer from other disorders that may cause inadequate input.
        - Valproic acid can help by putting a brake on the activity of impulse generation by making the limbic system less active overall.
- Agitation in Dementia
    - Cognitive decline and deficits social competence are known to be the hallmarks of dementia. however 80-90% of patients with dementia are also known to suffer from psychological symptoms and abnormalities in behavior; including verbal and physical aggression or agitation (Muller, 2003).
    - Valproic acid's efficacy is limited in this patient population. Research has shown that it has a Number Needed to Harm (NNH) of 26, harm was defined as death within 6 months, making its use risky.
    - Divalproex Sodium for agitation in dementia (Porsteinsson, 2001)
        - Pharmacotherapy treatment for agitation in dementia is considered when agitation is refractory to the removal or reversal of things that may have precipitated the agitation.
        - Previous studies have shown that carbamazepine (another anticonvulsant) may be efficacious for this behavioral problem. However, this drug is known for causing certain drug-drug interactions making it risky for patients that may be taking other medications concurrently. In light of this, the authors of this study explored the efficacy and tolerability of other anticonvulsants. This study looked at the potential of divalproex sodium in patients with dementia and agitation and assessed its efficacy, tolerability, and safety.
        - The study consisted of 56 participants, and took place over 6 weeks at 7 long term care facilities. Participants were considered eligible if they met criteria for 1) alzheimer's disease, 2) vascular dementia or 3) mixed dementia. Participants were >60 years old and had shown symptoms of agitation for a minimum of 2 weeks. They were then treated with either a placebo or divalproex sodium.

Agitation was measured by the agitation factor of the Brief Psychiatric Rating Scale (BPRS) and by Clinical Global Impression (CGI).

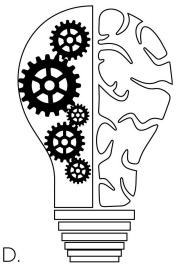
- Results found **no significant difference in total scores between groups** on the BPRS or CGI. However, **those in the divalproex group were found to have more side effects than placebo group (p = 0.03) some including stroke and seizures**.

Side effects:

- Neutropenia when used in conjunction with Clozapine (Malik, 2018)
  - Clozapine is the only evidence based medication in treating treatment resistant schizophrenia which affects about ⅓ of patients with schizophrenia. Clozapine is shown to be effective in treating 60-70% of these patients and is associated with a long term decrease in mortality. Despite this success clinicians continue to be wary of its use due to the feared adverse effect of neutropenia.
  - A case control study was conducted to identify any concurrent medications used with clozapine that may increase the risk of neutropenia. 136 cases of clozapine induced neutropenia were matched with 136 controls and looked at a variety of medications: antidepressants, beta-blockers, other antipsychotics and valproate to determine risk of neutropenia.
  - The study found that valproate was associated with significantly increased odds of neutropenia (**OR = 2.28**, 95% CI: 1.27-4.11, p = .006). The risk of neutropenia was also found to be dose dependent, where a higher dose of valproate had a higher risk of neutropenia when compared to a lower dose.
- Pancreatitis
- Hepatotoxicity
  - One of the effects of valproic acid is to inhibit the urea cycle making it a contraindication for its use in patients with a urea cycle disorder (inherited disorder where they cannot attach ammonia to make urea). At baseline these patients likely have an elevated ammonia level and if given valproic acid it may cause hepatic encephalopathy.
  - Elevated liver enzyme levels in patients with Hepatitis C (Felker, 2003)
    - One of the feared adverse effects of valproate is hepatotoxicity as it can be fatal. Due to this valproate use in patients with **any form of hepatic dysfunction is usually avoided**.
    - Psychiatric disorders are known to be prevalent in patients with hepatitis C and valproate use is usually avoided in these patients due to the fear of fatal



hepatotoxicity when it would usually be the treatment of choice for these patients.
    - This study compared baseline and follow up ALT levels in patients with positive hepatitis C status who were taking valproate to those taking other medications (lithium or gabapentin, or antidepressants).
    - Study found no significant difference between these groups. Although there was an increase in ALT levels in hepatitis C patients after starting valproate (7.9 %) there was also a similar increase in hepatitis C patients starting antidepressants (5.6%) or lithium/gabapentin (6.5%). This suggests that the elevation in ALT levels may be due to fluctuations in the hepatitis C disease rather than being due to the addition of valproate.
    - This study concluded that using valproate is a possibility for patients with hepatitis C, especially if it provides the best control for their psychiatric symptoms.
- **Severe Hyponatremia** due to valproic acid toxicity (Gupta, 2015)
    - This case report describes a rare case of a 54 year old woman with a history of bipolar disorder who presented with mental status change after intentionally ingesting 7,500 mg VPA. On examination she was found to have a serum sodium of 99 mEq/L (normal serum sodium range = 135-145), one of the lowest serum sodium levels ever documented, she was also found to have a low plasma osmolality (211 mOsm/kg H20). Her valproate level at presentation was 59.3 mg/L. This patient was bolused 2 L of IV saline, VPA was withheld, and was admitted to ICU for monitoring. Serum sodium levels were serially measured, after 36 hours VPA level fell to 22.8 mg/L and serum sodium increased to 125 mEq/L at this point she returned to her baseline mental state.
    - VPA is given as a sodium salt, due to this it can precipitate hypernatremia when given in large doses. However, long term use of VPA can cause chronically low sodium levels with correlated with this patients sodium level of 127 mEq/L a year prior. VPA is also known to be a cause of **syndrome of inappropriate antidiuretic hormone (SIADH)** which corresponds with this patient presentation. This report presents that this was a cause of acute on chronic hyponatremia due to VPA overdose.
    - Severe hyponatremia can have tragic consequences such as seizures, coma or death. While this patient showed improvement and had a favorable outcome, knowing this rare consequence of VPA toxicity is important to prevent tragic consequences for future patients.
- Never use in pregnant women



    - Aside from causing neural tube defects it can also cause a, 10 point decline in IQ, and doubles the rate of autistic spectrum disorder.

Drug Monitoring

- Therapeutic Drug Monitoring for Divalproex-ER (Reed, 2006)
    - Therapeutic drug monitoring of plasma anti epileptic drug (AED) concentrations is routinely used to determine if adjustments to dosage need to be made. Conventionally, the blood sampling time chosen is usually when the AED concentration is at its lowest (trough concentration).
    - Clinicians are accustomed to monitoring for the conventional AED formulations (valproate, divalproex) but have limited experience monitoring extended release AED formulations, specifically divalproex-ER which is intended to be taken once per day (either in the morning or evening). Trough sampling is best achieved right before a morning dose (prepose) however the optimal time to sample after an evening dose isn't clear.
    - The purpose of this study was to determine the optimal time to obtain a blood sample for plasma VPA concentration after a once-daily dose of divalproex-ER, given either in the morning of evening. The study analyzed the steady state plasma VPA concentration time profiles from 5 published divalproex-ER studies.
    - Results
        - When taking divalproex-ER in the AM: a blood sample taken 21-24 hours after the last divalproex-ER dose is expected to have plasma VPA concentrations within 3% of the trough value making this an optimal time to take blood sample.
        - When taking divalproex-ER in the PM: waiting 21-24 hours after last divalproex-ER dose is limited due to the fact that most labs would be closed by then. For patients dosed in the evening a blood draw 12-15 hours after last **dose will give a plasma VPA concentration that is 18%-25% higher than trough values.** However, waiting 18-21 hours will result in concentration values only 3%-13% higher than trough values, making this a more optimal time to take a blood sample.
    - Conclusion
        - Timing of blood sample does matter in order to properly interpret plasma VPA concentration.

Valproate reopens critical-period learning of absolute pitch (Gervain, 2013)

Episode 071: Valproic Acid: History, Mechanism, Treatment in Bipolar, Schizophrenia, Aggression and Side Effects with Dr. Cummings

Alex Ramos B.A., David Puder, M.D., Michael Cummings, M.D.

- Absolute pitch is the ability to identify or produce the pitch of a musical sound, individuals who have this can immediately recognize which note they hear and if a note is even a tiny bit out of tune. researchers have found that acquiring absolute pitch has a critical period. A critical period is a set amount of time usually early in a person's life where their experience has a lasting effect on how their brain functions and develops.
- Once these critical periods close they close the door for further change. researchers have found that the action of an enzyme called HDAC plays a role in closing this door and putting a brake on the critical period. Research has shown that inhibiting HDAC can reopen this critical period neuroplasticity in mice to enable recovery of amblyopia and allow for new forms of auditory learning.
- This study looked at valproate (which is known to inhibit HDAC) and its ability to promote **neuroplasticity**. This randomized, double blind study had 24 participants who were either received a placebo or valproate in the first treatment arm for 15 days. After a washout period of 2-4 weeks participants crossed over to the second treatment arm for another 15 days, if the participant took valproate in the first treatment arm then they took a placebo in the second and vice versa.
- In the first treatment arm participants were trained to associate 6 different musical pitches with six names (e.g., sarah, david, francine, jimmy, karen, leo). When they crossed over to second treatment arm they used 6 different pitch classes with 6 different names. Participants were then tested to determine their ability to recognize the proper name associated with the proper pitch.
- The study found those that had been given valproate first performed significantly better than those who were in the placebo group.

Valproic Acid, a molecular lead to multiple regulatory pathways (Kostrouchova, 2007)

- Valproic acid induces differentiation and inhibits proliferation of cultured cancer cells
    - Research has found that treatment of cholinergic neuroblastoma x glioma hybrid cell line (NG108-15) with valproic acid was shown to reduce the growth of these cells. It was also shown to reduce proliferation and differentiation of human neuroblastoma cells.
    - Long term treatment with valproic acid has also shown inhibition of prostate cancer cell growth both in vitro and in vivo.
- Valproic acid induces apoptosis in cultured cancer cells
    - Valproic acid was shown to induce apoptosis in human leukemia cell lines by triggering the release of cytochrome c from mitochondria and activating the caspase cascade that induces apoptosis.
- Valproic acid inhibits expression of angiogenic proteins in cultured cells

    - Treatment of colon adenocarcinoma cell line with valproic acid was shown to significantly reduce vascular endothelial growth factor secretion and downregulated its expression.
- Valproic acid affects cell behavior by multiple mechanisms including HDAC, MAPK signaling, beta-catenin-Wnt signaling and other pathways. These effects have shown valproic acid to be a powerful tool in gene expression and cell behavior.