DSH PSYCHOTROPIC MEDICATION
Operational Procedures
Valproic Acid/Divalproex Protocol

I. Indications:

A. At least one of the following clinical indications is present and documented in the chart:

1. Seizure disorders, including monotherapy and combined therapy in complex partial seizures, simple and complex absence seizures, myoclonic, and generalized tonic-clonic seizures as well as adjunctively in individuals with multiple seizure types that include absence seizures.

2. DSM diagnosis of bipolar disorder or schizoaffective disorder, especially for rapid cycling and mixed episodes, including first line or adjunctive medication for acute mania and for maintenance therapy.

3. Severe persistent self-injurious behavior with evidence that a behavioral treatment, as part of a formal treatment program, was adequately implemented and found to be ineffective; and less toxic pharmacological interventions including antipsychotics have been tried.

4. Acute phase of schizophrenia or schizoaffective disorder, as an adjunct to an antipsychotic agent in individuals who fail to respond to an adequate trial of the antipsychotic agent alone, for whom clozapine is not appropriate, particularly in schizophrenia or schizoaffective disorders with aggressive or impulsive behavior. Need for continued valproic acid treatment should be reassessed after acute stabilization in schizophrenia.

5. Aggressive impulsive behavior in individuals with an underlying seizure disorder, intermittent explosive disorder, severe antisocial and borderline personality disorders, conduct disorder and dementia (less effective than antipsychotics).

6. Migraine prophylaxis.

II. Contraindications:

A. Hypersensitivity to the drug.

B. Preexisting unstable hepatic disease or significant hepatic dysfunction.

C. Known urea cycle disorders (hyperammonemic encephalopathy, persistent hyperammonemia). Note that elevated plasma ammonia may induce irritability and psychomotor agitation. If irritability and psychomotor agitation increase with addition of valproic acid or divalproex, consideration should be given to measuring plasma ammonia.

D. Preexisting thrombocytopenia, with a platelet count < 100K per mm^3. Risk of bleeding typically begins at platelet counts of < 50K platelets per mm^3.

E. Preexisting clinical presentation consistent with active pancreatitis.

III. Precautions (risk/benefit analysis supports use):

A. Pregnancy or breast feeding. Associated with neural tube defects and decrements or delays in cognitive development or performance, as well as a doubling of the risk for neurodevelopmental disorders. Among men with epilepsy, valproic acid exposure is associated with reduced sperm count and motility, as well as an increase in abnormal sperm. On 1/12/24, the European Medicine Agency's safety committee recommended precautionary measures to address a potential risk of neurodevelopmental disorders (NDD) in children born to men prescribed valproate during spermatogenesis; however, this recommendation was based on unpublished data. To date, published data has not identified an increased risk of NDD in the offspring of men prescribed valproate.

B. Individuals exhibiting significant baseline abnormalities in blood counts or receiving other potentially myelotoxic agents or with a history of adverse hematological reaction to any drug should be considered at special risk.

[NOTE: Thrombocytopenia with platelet count <100K platelets per mm^3 is *absolute contraindication*.]

C. Renal disease or impairment (dose correction may be needed).

D. Individuals with congenital metabolic disorders and/or organic brain disease require caution in use, especially in combination therapy in higher risk Individuals with acute pancreatitis or history of chronic or subacute pancreatitis.

F. Elderly individuals (over 65 years of age), with excessive somnolence and/or with decreased food or fluid intake.

IV. The following initial workup and follow-up are completed:

A. There is informed consent or alternate legal authorization.

B. There is chart documentation of discussion with Individual or guardian regarding risk of teratogenic effects in females if individual becomes pregnant.

C. Initial work up includes:

1. Complete blood count (CBC) with differential, including platelet count, liver function tests, and ECG. All labs, except ECG, should be obtained within 30 days of medication initiation. ECG should be obtained within one year. Note that pre-treatment laboratory evaluation does not apply to patients admitted on a stable valproic acid treatment regimen.

2. Pregnancy test for females of childbearing potential within 30 days before drug initiation.

3. Weight, BMI (body mass index) and waist circumference within 30 days.

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D. Monitoring:

1. Valproic acid (VPA) plasma concentrations should be measured 4 to 7 days after dose changes, e.g. during titration or adjustment.

2. Additionally, plasma concentrations should be checked every 6 – 12 months or as clinically indicated.

3. The trough period for immediate and DR formulations is 12 hours post dose, while the trough for the ER formulation should be measured 18 to 24 hours post dose. Note that the extended-release formulation requires 22 to 23 hours to complete absorption and produces a nearly flat kinetic curve, meaning that time of dosing matters very little. Alternatively, dividing a 12-hour trough of the extended-release formulation by a factor of 1.3 provides a reasonably accurate estimate of the true trough concentration.

4. In the first 6 months of VPA treatment, CBC, including platelets and LFTs should be measured monthly. Note that this does not apply to patients admitted on an extant stable valproic acid treatment regimen. They should be treated as those taking valproic acid or divalproex for more than 6 months.

5. After the first 6 months of VPA treatment, CBC including platelets and liver functions should be monitored every 6 – 12 months or as clinically indicated.

6. The ECG should be monitored annually or as clinically indicated.

Monitoring Summary Table:

MONITORING POINTS	MONITORING TESTS
Pre-treatment baseline	CBC with differential, including platelets, LFTs, Pregnancy test, ECG (past year)
Monthly up to 6 months	CBC with differential, including platelets and LFTs
From 6 months onward	CBC with differential, including platelets, LFTs, VPA plasma concentration and ECG (annually) every 6 – 12 months or as clinically indicated

7. Physician and nursing staff should be at heightened awareness of possible pancreatitis.

8. Weight, BMI, and waist circumference are monitored at least every 6 months.

9. Annual physical examination of female individuals. Consider possibility of polycystic ovary disease (there is controversial association with Valproic acid/divalproex treatment).

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V. Dose initiation, titration and discontinuation:

Note: Valproic acid begins absorption immediately after ingestion. This is sometimes responsible for acid reflux or dyspepsia.

Divalproex (Depakote delayed release®) typically is not hydrolyzed to valproic acid until reaching the distal stomach and proximal small bowel. Other than this slight delay, however, its kinetics are identical to that of valproic acid (Depakene®).

Divalproex extended release (Depakote ER®) is divalproex imbedded in a wax matrix, resulting in gradual release throughout the bowel and relatively stable plasma concentrations for circa 22 hours. It is the only preparation specifically designed for once per day dosing.

Note that the other formulations may permit seizure when there is underlying epileptiform activity or a significantly lowered seizure threshold is present if dosed once per day due to the wide variation between peak and trough plasma concentrations.

Valproic acid is > 90% protein bound. This means that at plasma concentrations of < 50 mcg/mL, there is essentially no free fraction and, hence, no drug is available to enter the brain. As total plasma concentrations exceed 100 mcg/mL, the relative proportion of drug in the free fraction pool increases. In cases where there are either absence of effects or signs of dose-related toxicity despite total plasma concentrations within therapeutic ranges, measurement of free plasma valproic acid may be helpful.

A. Seizure disorders:

1. The typical initial dose of 10 – 15 mg/kg/day is given in two to three divided doses (once daily for the extended release formulation). The dosage is increased by 5 – 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day.

2. In the elderly, the starting dose may need to be decreased due to a decrease in unbound clearance of valproate and possibly a greater sensitivity to somnolence. Dosage is increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events.

3. Dose reductions or discontinuation are considered in individuals with decreased food or fluid intake and in individuals with excessive somnolence. The ultimate therapeutic dose is achieved on the basis of both tolerability and clinical response.

4. Serum levels are monitored to find adequate dose. Serum trough levels are obtained after 4 to 7 days at any given dosage. The extended release formulation requires 5 to 7 days to reach steady-state.

5. Trough levels are drawn in the morning before the AM dose.

6. A plasma level of 50 – 100 mcg/mL is usually obtained for adequate therapeutic response. The benefit of improved seizure control with higher levels is weighed against the possibility of a greater incidence of adverse reactions.

B. Bipolar and schizoaffective disorders (or other psychiatric indications)

1. The typical initial dose is 750 mg in divided doses (once daily in extended-release formulation), then titrating up or down depending on the plasma level to achieve the lowest therapeutic dose. A loading dose of 20 – 30 mg/Kg/day may be used in cases of severe manic or mixed states.

2. Elderly individuals typically receive doses nearly half that of younger adults.

3. Plasma levels are monitored to find adequate dose. Serum trough levels are obtained after 4 to 7 days at any given dosage.

4. Trough levels are drawn 12 hours after the previous dose, usually in the morning before the AM dose.

5. A plasma level of 80 – 120 mcg/mL is usually obtained for adequate symptom relief.

C. Drug-drug interactions are accounted for:

1. The dosage of valproic acid or divalproex is modified due to co-administration of other drugs:

a. Dose of valproic acid or divalproex may need to be increased when co-administered with other drugs that induce metabolism, increase clearance (and decrease levels) of valproic acid or divalproex. The inducers include: phenobarbital, primidone, phenytoin, carbamazepine, lamotrigine, ethosuximide, and rifampin. Lamotrigine and oxcarbazepine may have milder effects.

b. Caution is used when valproic acid or divalproex is co-administered with antiretroviral treatment (some of these medications can be inducers and others may be inhibitors of valproic acid or divalproex metabolism).

c. Dose may need to be decreased when co-administered with other drugs that are inhibitors of valproic acid or divalproex metabolism and/or decrease protein binding (e.g. aspirin/salicylates, cimetidine). Fluoxetine may have similar effects in some cases.

2. Dosage of other drugs may need to be modified due to co-administration of valproic acid or divalproex metabolism. Divalproex appears to inhibit glucuronidation enzymes (glucuronyltransferases) and CYP2C9 and may cause clinically relevant interactions due to protein displacement:

    a. Levels of phenobarbital, phenytoin, carbamazepine, oxcarbazepine, and ethosuximide levels are followed closely in cases of adding or discontinuing valproic acid or divalproex since valproic acid or divalproex may increase their levels.

    b. Lamotrigine dose adjustments are carefully implemented in accordance with lamotrigine policy in case of co-administration.

    c. Divalproex or valproic acid may increase levels of several benzodiazepines (e.g., diazepam).

    d. Caution is used when using clonazepam with valproic acid or divalproex because it may result in absence seizures, including status epilepticus.

    e. Caution is used when some antidepressants and antipsychotics are co-administered due to possible interaction. In some cases, it is thought that the interactions contributed to toxicity and in other cases, it was difficult to establish causal relationships. It has been reported that risperidone may increase valproic acid or divalproex levels by displacement from plasma proteins and the co-administration may cause edema. There is relatively good agreement that tricyclic antidepressant levels increase by 50 – 60% after adding valproic acid or divalproex.

    f. Careful monitoring of INR is required when warfarin is used in combination with valproic acid or divalproex. Valproic acid or divalproex can displace warfarin from protein binding.

VI. Possible adverse reactions:

A. Hepatotoxicity, which can be fatal (usually occurring within the first six months). Symptoms include lethargy, malaise, anorexia, jaundice and weakness.

B. Hyperammonemia and hyperammonemic encephalopathy, which can be fatal and can occur in individuals with urea cycle disorders (uncommon). Elevated plasma ammonia also may cause irritability and psychomotor agitation. Consider obtaining a plasma ammonia measurement if this is suspected.

C. Pancreatitis (risk does not correlate with dose).

D. Thrombocytopenia (risk factors include dose, age above 65, duration of dose). The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 mcg/mL in females and 135 mcg/mL in males.

E. Gastrointestinal symptoms, including nausea, vomiting, dyspepsia, abdominal pain, diarrhea, anorexia, and constipation. The risk decreases overtime especially if the drug is taken with food. Consider switching from other forms to enteric-coated or slow release forms.

F. Weight gain (10% occurrence with average of 5.5 pounds).

G. Nervous system, including somnolence, tremor, dizziness, diplopia, amblyopia/blurred vision, ataxia, nystagmus, emotional lability and amnesia.

H. Respiratory system, including flu syndrome, infection, bronchitis and rhinitis.

I. Other, including teratogenic effects, alopecia, nail pigmentation, edema and weight loss.

J. Possible, but controversial association with polycystic ovary disease.

K. Valproate ketometabolites are eliminated in urine and may contaminate urine ketone test.

L. Suicidal ideation.

VII. Additional Considerations

Obtain and monitor ammonia and glutamine levels if individual has:

A. History of unexplained encephalopathy or coma, encephalopathy associated with a protein load, unexplained mental retardation or elevated ammonia or glutamine.

B. Cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN or protein avoidance.

C. Some authors have suggested that chronic valproic acid or divalproex treatment may impair bone metabolism. Weight-bearing exercise and reasonable sunlight exposure may mitigate risk. Additionally, vitamin D supplementation and calcium supplementation may warrant consideration in persons at elevated risk for osteoporosis or osteopenia. Typical doses of calcium and vitamin D in patients at risk are 1200 mg/day and 800 units/day, respectively. Measurement at baseline and following one month of supplementation would be prudent to assure adequate treatment. Thereafter measurements could be obtained as clinically indicated. Periodic bone density measurements, e.g. annually to every five years depending on age, gender, and other risk factors, may assist in identifying evolving osteoporosis or osteopenia.

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