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Adjunctive Valproic Acid for Delirium and/or Agitation on a Consultation-Liaison Service: A Report of Six Cases

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The authors present six cases in which valproate was used in patients seen by a consultation-liaison service (CLS) to manage delirium and/or psychotic agitation. The intravenous (IV) preparation (Depacon, Abbott Laboratories) was used in two nothing by mouth (NPO) patients, while the liquid oral preparation (Depakene, Abbott Laboratories) was used via nasogastric tube (NGT) in the other patients. All of these cases had suboptimal responses and/or concerning side effects from conventional therapy with benzodiazepines and/or antipsychotics. In all six cases, the CLS use of valproic acid combined with conventional antidelirium medications resulted in improved control of behavioral symptoms without significant side effects from valproic acid. Consultation-liaison psychiatrists should consider the addition of valproic acid to control behavioral symptoms of delirium when conventional therapy is inadequate. This may be especially advisable when problematic side effects result from more conventional psychopharmacological management. Specifically, intravenous valproate sodium may be a viable option for NPO patients.

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Consultation-liaison psychiatrists are frequently confronted with cases where dangerous agitation compromises the patient's immediate safety and eventual recovery from medical/surgical illness. In addition, many such patients are NPO, which severely limits psychopharmacological options to intramuscular/intravenous (IM/IV) antipsychotics and/or benzodiazepines. These two medication classes are often used in combination for a synergistic effect. However, there are cases when these choices present significant problems. Antipsychotic agents may be associated with extrapyramidal symptoms (EPS), or more rarely, neuroleptic malignant syndrome (NMS) and prolongation of the QTc interval and torsade de pointes.[1] Benzodiazepines may excessively sedate the patient (precluding accurate mental status assessment) and increase cognitive impairment, and concerns have been raised regarding their safety in patients with respiratory compromise. In addition, lorazepam, a frequently used benzodiazepine in consultation-liaison practice, has a relatively short half-life, requiring frequent redosing. We have recently treated six cases where treatment with antipsychotic agents and/or benzodiazepines was associated with either suboptimal clinical response or concerning side effects. All of these cases were substantially helped by the adjunctive use of valproic acid combined with other psychotropic agents.

Case 1

A 45-year-old white male with a history of alcohol dependence presented acutely to the medical center with abdominal pain. He was found to have peritonitis and underwent emergency laparotomy. A 4 cm×5 cm gastric ulcer was discovered, and an antrectomy and gastrojejunostomy were performed. Three days postoperatively, he developed respiratory distress and hypoxia, which required intubation. He developed ventricular fibrillation and responded to cardiac defibrillation, lidocaine, and atropine with restoration of normal sinus rhythm. He also had pulmonary mucous plugs, which further compromised his respiratory status and required several bronchoscopies for removal. During this period,

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he developed episodic agitation. With minimal success, he received trials of midazolam, diazepam, lorazepam, morphine, fentanyl, haloperidol, and vecuronium in various combinations in attempts to control his agitation. Haloperidol was subsequently discontinued due to QTc prolongation. Twelve days postoperatively, he was noted to have developed an enterocutaneous fistula, which required an extended period of NPO status and a prolonged course of IV antibiotics. He was also found to have an infected intravenous catheter line.

Psychiatry consultation was obtained for assistance in management of a variable level of consciousness (LOC), intermittently agitated/disruptive behavior, altered sleep/wake cycle, and auditory and visual hallucinations. Laboratory data at the time of consultation included Na + 134 meq/liter, K + 3.2 meq/liter, glucose 178 mg/dl, normal BUN/Cr, WBC 22.0 K/mm^3, Hgb 9.1 g/dl, Hct 26.9%, and platelets 438 K/mm^3. Psychiatric examination revealed variable LOC, impaired and fluctuating cognitive status, intermittent behavioral agitation (e.g., pulling against his restraints), orientation to person and time only, thought disorganization, persecutory delusions, and auditory and visual hallucinations. He was diagnosed with delirium, multifactorial, with likely contributing factors, including infection, pain medications, anemia, and respiratory compromise. Due to his continued delirium, IV valproate sodium (Depacon, Abbott Laboratories) was started at a dose of 500 mg bid on postoperative day 21. Lorazepam 1 mg IV qid was administered along with IV valproate sodium. Midazolam, diazepam, and morphine were discontinued.

Within 3 days, the patient was notably less agitated and more cognitively organized, with intact orientation in three spheres, in short-term memory, and in concentration. Lorazepam was thereafter tapered. His delirium subsequently completely resolved, and his cognitive status normalized, with a Mini-Mental State Exam (MMSE) score of 29/30 recorded on postoperative day 31. A serum valproate level was 29mg/liter, and aspartate aminotransferase/alanine aminotransferase (AST/ALT) were unremarkable. The next day, he was taking food and po medications. Intravenous valproate sodium was then discontinued, and oral divalproex sodium 500 mg po bid was started.

Case 2

A 47-year-old white male with a history of esophageal carcinoma, status-postesophagectomy with gastric pull-up, radiation therapy, two cycles of chemotherapy, aspiration pneumonitis, persistent fevers, pulmonary edema, hepatitis C, and peptic ulcer disease was admitted following an upper gastrointestinal hemorrhage, with hematemesis, anemia, and hypotension. The patient underwent embolization of an intercostal artery and transfusion, with a posttransfusion hematocrit of 30%. He was treated with IV antibiotics and antifungal agents for enterococcus bacteremia and disseminated candida. He required intubation and ventilatory support. He had a long history of PTSD following combat and prisoner-of-war experiences 30 years previously, for which he had taken fluoxetine.

After 11 days of hospitalization in the intensive care unit (ICU), the patient was referred to psychiatry for episodic agitation, alternating with sedation and a fluctuating level of consciousness. His mental status made it difficult to wean him from ventilatory support. At the time of the psychiatric consultation, he was receiving lorazepam 1 mg IV q 1 hour and hydromorphone 6 mg q 1 hour, with *pro re natas* (PRNs) of morphine, midazolam, and Inapsine. Laboratory data at the time of consultation included normal Na + , K + , and BUN/Cr, glucose 115 mg/dl, WBC 6.0 K/mm^3, Hgb 10.2 g/dl, Hct 30.4%, and platelets 269 K/mm^3. On psychiatric examination, he was intubated and somnolent, with nursing staff reports of sleep cycle disruption. A full mental status assessment could not be accomplished. The patient was diagnosed with delirium, multifactorial, with contributing factors, including infection with recurrent fevers, pain medications, anemia, and respiratory compromise. He was started on haloperidol 2.5 mg IV q 8 hours and diazepam 5 mg IV q 6 hours, and lorazepam was discontinued. His agitation was somewhat decreased, and he was able to answer simple questions by mouthing words.

He was continued on IV antibiotics, and a tracheostomy was performed. However, his intermittent agitation and variable LOC still interfered with ventilator weaning. In addition, he continued to require frequent PRN doses of lorazepam, morphine, and midazolam to control breakthrough agitation. Haloperidol was increased to 5 mg IV q 6 hours. Due to continued agitation despite this multidrug regimen, he was started on a trial of adjunctive liquid valproic acid (Depakene, Abbott Laboratories) 250 mg per nasogastric tube (NGT) q 6 hour on hospital day 29. Diazepam was discontinued. Following the emergence of a prolonged QTc interval, haloperidol was discontinued on hospital day 32.

Within 4 days of starting valproic acid, his agitation was much reduced and level of consciousness improved. Despite his continued state of being nonverbal, he was much better able to attend to his environment and respond to examiner questions. Valproic acid was increased to 250 mg tid plus 500 mg qhs, which yielded a serum valproate level of 53 mg/liter. His agitation was under much better control, and he was better able to communicate.

Case 3

A 50-year-old white male with a history of morbid obesity, chronic obstructive pulmonary disease, hypoventilation syndrome, sleep apnea, reactive airway disease, congestive heart failure, diabetes mellitus, deep venous thrombosis, and pulmonary embolus with Greenfield filter placement was admitted following further compromised respiratory status. He also had a history of posttraumatic stress disorder (PTSD), substance dependence, and depressive disorder. He was intubated, treated with antibiotics and corticosteroids with initial improvement and was then extubated. He then deteriorated and experienced respiratory arrest, requiring cardiopulmonary resuscitation (CPR) and reintubation. The patient was transferred to the medical center for definitive management. After transfer, he continued to require aggressive ventilatory support. A sputum sample revealed pseudomonas aeruginosa and he received a course of cefepime and ciprofloxacin. He also experienced a gastrointestinal (GI) bleed, which required several transfusions to maintain a hematocrit of 27%.

He was treated with diazepam 20 mg IV q 4 hours, fluphenazine 5 mg per NGT q 6 hours, and paroxetine 40 mg per NGT qd. Despite this regimen, he required frequent doses of PRNs of midazolam and lorazepam to control breakthrough agitation, including pulling out his indwelling lines, and morphine for pain. He was referred to psychiatry for agitation and psychosis. At the time of consultation, laboratory data included normal Na+, K+, and BUN/Cr, glucose 145 mg/dl, WBC 8.1 K/mm^3, Hgb 10.1 g/dl, Hct 31.0%, and platelets 659 K/mm^3. On psychiatric examination, he had a variable level of consciousness (LOC) (alternately somnolent and agitated), psychotic symptoms (hallucinations), and confusion. He would nod and shake his head in response to questions. He was oriented in three spheres, but displayed perplexed and blunted affect. He was diagnosed with delirium, multifactorial, with infection, pain medications, anemia, and respiratory compromise as likely contributing factors. He was begun on liquid valproic acid (Depakene, Abbott Laboratories), 575 mg per NGT tid; risperidone, 2 mg per NGT q 6 hours; lorazepam, 2 mg per NGT q 6 hours; and sertraline, 50 mg per NGT qd. Fluphenazine, paroxetine, and diazepam were discontinued.

The patient's agitation was substantially decreased. His sleep pattern improved, and lorazepam was discontinued. Serum valproate level was 36 mg/liter. Risperidone was discontinued after a QTc was noted to be 470 msec. His valproic acid dose was increased to 650 mg per NGT tid, and sertraline was increased to 150 mg per NGT qd. His agitation remained under control. His anxiety decreased, and his mood and affect were substantially improved. He was eventually able to tolerate ventilator weaning trials without agitated behavior.

Case 4

A 40-year-old male suffered acute mental status changes following an episode of community-acquired pneumonia. The patient developed respiratory compromise that led to his admission and required mechanical ventilation. His medical history also included fever of unknown origin, obstructive sleep apnea, obesity hypoventilation syndrome, diabetes mellitus type II, pansinusitis, and pulmonary embolism. He also had a history of bipolar disorder, but his psychiatric symptoms had been under control for 20 years (with no psychiatric hospitalizations and no notable episodes of depression or mood elevation) on a stable dose of lithium carbonate (900 mg bid with a serum level of 0.7 mmol/liter). He had a serious dystonic reaction to haloperidol in the distant past.

His level of agitation was noted by nursing staff to increase as his fever recurred, and he required PRNs of morphine for pain. He had a psychiatric consultation initiated for a "waxing and waning level of consciousness" with intermittent agitation alternating with periods of excessive somnolence. Laboratory data at the time of consultation included normal Na+, K+, and BUN/Cr, glucose 184 mg/dl, WBC 6.7 K/mm^3, Hgb 11.1 g/dl, Hct 34.0%, platelets 238 K/mm^3, and NH4 + 38 μmol/liter. On examination, he was sedated, briefly arousable, and could follow simple directions. He was diagnosed with delirium, multifactorial. Possible contributing contributing factors included infection, medications, anemia, and respiratory compromise. Because of concern for the risk of electrolyte disturbances due to his medically compromised condition and its potential

effects on serum lithium levels, lithium carbonate was discontinued and liquid valproic acid 750 mg (Depakene, Abbott Laboratories) per NGT tid was started. An initial serum valproate level was 30 mg/liter. Due to some continued agitation, his valproic acid dose was increased to 750 mg q am, 750 mg q pm, and 1000 mg q hs. A subsequent serum valproate level was 52 mg/liter.

On this valproic acid dose, the patient's agitation was improved, and he required less frequent PRNs for acute control, but he still had occasional episodes of agitation and variable LOC. Risperidone, 2 mg per NGT q 6 hours, and lorazepam, 1 mg per NGT q 6 hours, were added. He had no further episodes of agitation, and at no point did he appear to experience a mood episode. On this combined regimen, his cognitive status gradually cleared, and his level of consciousness normalized.

Case 5

A 41-year-old white male with a history of polysubstance dependence was referred for agitated and disorganized behavior following a motor vehicle accident that resulted in multiple orthopedic injuries. He also had acute respiratory distress, fevers, and anemia. Following culture results, his diagnoses included *streptococcus pneumoniae pneumonia* and *staphylococcus aureus bacteremia*. He was confused, pulled the IV lines, removed himself from an orthopaedic traction device, and fought restraints. He was receiving PRNs of midazolam and fentanyl, but his behavior continued to be agitated. He required intervention by five police officers to contain his behavior.

Psychiatric consultation was ordered for evaluation of altered mental status. At the time of psychiatric consultation, laboratory data included normal Na+, K+, and BUN/Cr, glucose 115 mg/liter, WBC 20.4 K/mm^3, Hgb 9.9 g/dl, Hct 28.6%, platelets 280 K/mm^3, total bilirubin 1.4 mg/dl, and AST 71 U/liter. On examination, he was disoriented and tangential with inappropriate answers to interview questions. He was agitated, fought against restraints, and tried to leave his bed despite implanted orthotic traction. He insisted on leaving the medical center and returning home. His affect was anxious and labile. His speech was loud, rapid, and pressured. The patient exhibited a variable LOC and variable levels of cognitive function. Insight into his clinical situation and judgment was poor. His score on the Mini-Mental State Exam (MMSE) was 2/30. Notably, he had no evidence of cognitive impairment prior to his motor vehicle accident. He was diagnosed with delirium, multifactorial. Possible contributing factors included infection, pain medications, anemia, and protracted substance withdrawal. He was initially treated with high doses of haloperidol IV (10 mg, 20 mg, and 30 mg in 1 hour intervals) but continued to be very agitated and confused, alternating with periods of decreased level of consciousness.

The patient's medication regimen was modified, and he was subsequently started on haloperidol, 10 mg IV qid; lorazepam, drip 3 mg IV/hour; and liquid valproic acid (Depakene, Abbott Laboratories), 250 mg per NGT bid 5 days after initial psychiatric consultation. His lorazepam drip was later discontinued, and diazepam 15 mg tid was started. His agitation decreased substantially within 3 days. Within 8 days of starting valproic acid, his agitation was resolved; his mood was improved; and his MMSE score was 26/28. Diazepam was slowly tapered from 15 mg tid to 5 mg tid, and haloperidol was discontinued. His delirium did not recur and his mental status was stable. Valproic acid was continued throughout this period.

Case 6

A 63-year-old undomiciled white male with a history of paranoid schizophrenia was hospitalized for a distal esophageal rupture, which rendered him NPO. He was referred to psychiatry for a variable level of consciousness, intermittent agitation, and paranoid psychosis (observed as suspiciousness and assaultive behavior) that profoundly interfered with his ability to cooperate with examination and treatment. He had refused placement of a chest tube and esophageal surgery. Laboratory data at the time of consultation included normal Na+, K+, and Cr, BUN 31 mg/dl, albumin 2.7*g*/dl, normal alkaline phosphatase, AST, ALT, and bilirubin, WBC 3.7 K/mm^3, Hgb 6.8 g/dl, Hct 22.4%, and platelets 361 K/mm^3. On examination, the patient was grossly paranoid and unable/unwilling to answer questions. He was diagnosed with psychotic disorder, not otherwise specified, and delirium, multifactorial with infection, pain medications, and anemia were all ruled out as possible contributing factors. He was started on haloperidol, 5 mg IV qhs, and over a period of 2 weeks, the dose was increased to 5 mg IV qam and 10 mg IV qhs. However, he continued to be hostile and intermittently agitated, either demanding that physicians and other medical personnel leave the room immediately upon entering or refusing to speak at all.

Due to the patient's fluctuating level of consciousness

and inability to display understanding of his illness and treatment options, he was found to lack capacity for operative consent. This led to a prolonged period of NPO status, during which psychopharmacologic options were limited. To more specifically address his agitation and irritability without potentially compromising his LOC with benzodiazepines, IV valproate sodium (Depacon, Abbott Laboratories) 250 mg bid was added to his haloperidol IV. His IV valproate sodium dose was adjusted gradually upward to 500 mg IV q6 hours. Although serum valproate levels remained in low therapeutic to subtherapeutic range even on the higher dose (from 33 to 53 mg/liter), within 5 days of starting valproate sodium, both surgical and internal medicine physicians noted the patient to be less agitated and more cooperative with physical examinations and procedures. His mood lability and hostility were also improved, and he became able to communicate with his treatment team, albeit to a limited degree.

DISCUSSION

Valproic acid was originally developed as an anticonvulsant. It acts by increasing the availability of gamma-amino butyric acid (GABA), a ubiquitous inhibitory neurotransmitter.[2] Its half-life is from 9 to 16 hours, and the oral and IV doses are equivalent.[2] Its recommended initial dosing is 10–15 mg/kg/day bid or tid.[3] The recommended serum trough level is 50–100 mg/liter.[3] Side effects include alopecia, tremors, thrombocytopenia, pancreatitis, hepatic toxicity, and somnolence.[2,3] Valproic acid has a high risk for teratogenicity (neural tube defects) and thus should be used with great caution, particularly during pregnancy.[3] Intravenous valproate sodium may be associated with less nausea than PO forms of valproic acid.[4]

Several studies have examined the safety and clinical effectiveness of rapid IV valproate sodium for seizure disorders. Devinsky et al. studied IV valproate sodium in 318 seizure disorder patients.[5] The median dose was 375 mg infused over 1 hour; the median number of doses was four, administered over a period of 2 days.[5] Headache, reaction at injection site, and nausea were each observed in 2% of patients.[5] Vital signs were not affected. Giroud et al. gave an initial injection of 15 mg/kg valproate sodium followed by a 5- to 6-hour infusion of 1 mg/kg/hour to reverse status epilepticus in three patients.[6] There was no impairment in concentration and no cardiovascular or respiratory complications.[6] Naritoku and Mueed gave infusions of IV valproate sodium at either 20 or 50 mg/min in 20 patients with epilepsy.[7] Three cases experienced notable side effects, each with vomiting, dizziness and nausea, and hypotension.[7] Venkataraman and Wheless studied 21 seizure patients with IV valproate sodium doses from 21 to 28 mg/kg at infusion rates of 3 or 6 mg/min.[8] No changes in blood pressure, electrocardiogram (ECG), or mental status were noted.[8] Transient pain occurred at the injection site in five patients.[8] Limdi and Faught studied 20 patients with seizure disorder with 20 mg/kg loading doses of IV valproate sodium administered at between 33.3 and 555 mg/min (median 200 mg/min).[9] No patient suffered a change in mental status or respiratory function, and two had significant decrease in blood pressure requiring the administration of vasopressors.[9]

Valproic acid has become increasingly popular in the psychiatric literature for treatment of bipolar disorder. In addition, it has been used for other aggressive and agitated states due to central nervous system (CNS) trauma, dementia, and other neurodegenerative disorders.[10–12] There have been reports of its utility in the treatment of alcohol withdrawal delirium.[13,14] Because valproic acid may decrease agitated behavior without necessarily decreasing levels of consciousness, it represents an attractive choice for the management of delirium, especially when there are suboptimal response and/or problematic side effects with benzodiazepines and/or antipsychotics. In addition, the IV form (Depacon, Abbott Laboratories) makes valproate sodium a viable choice for patients who are NPO or otherwise unable to swallow oral medications.[15,16]

There have been case reports describing the use of IV valproate sodium and oral divalproex sodium for specific psychiatric illnesses. Kruger and Braunig successfully treated a patient with severe catatonia with an initial 24-hour dose of 4,000 mg IV valproate sodium.[16] The patient was ultimately maintained on 900 mg/day oral valproic acid. Kaltsounis and De Leon controlled a manic episode in a schizoaffective disorder patient who had undergone a gastric bypass operation with 2,500 mg IV valproate sodium q 12 hours.[15] Herbert and Nelson treated an elderly patient with a manic episode with IV valproate sodium 200 mg q 6 hours.[17] Hilty et al. treated behavioral agitation in a pediatric case of autism with a single infusion of 2,000 mg IV valproate sodium followed by 1,000 mg valproic acid po bid.[18] Norton described the successful use of IV valproate sodium to con-

trol three cases of acute mania.[19] The three cases were treated with two doses of 1,000 mg IV valproate sodium (four hours later) followed by 1,000 mg PO valproic acid bid on subsequent days.[19]

Grunze et al. successfully treated seven bipolar disorder type I patients with IV valproate sodium.[20] Five of the patients were in manic episodes, four of whom recovered. The two depressed patients did not improve substantially with IV valproate sodium. The doses of IV valproate sodium used in the manic patients ranged from 1,800 mg/day to 3,600 mg/day with a mean dose of 2,400 mg/day. Erfurth and Grunze treated an otherwise treatment refractory manic patient with IV valproate sodium.[21] Curiously, their patient had not responded to oral valproic acid doses of 3,600 mg/day, which gave a serum level of 108 mg/liter. Eventually, combination therapy of IV valproate sodium (1,800 mg/day, serum levels 44.3–75.4 mg/liter) plus lithium carbonate and gabapentin was successful in controlling the manic episode.

Norton and Quarles reported three cases of the use of IV valproate sodium.[2] One case was an agitated Alzheimer's disease patient who responded to IV valproate sodium 500 mg bid (serum level 62 mg/liter). Their second case was a bipolar disorder patient (with recent neuroleptic malignant syndrome) in an acute manic episode that responded to IV valproate sodium 500 mg tid (serum level 72 mg/liter). Their final case was a manic patient who was controlled with IV valproate sodium 500 mg bid (serum level 91 mg/liter). Porsteinsson et al. completed a placebo-controlled study of oral divalproex sodium for agitated dementia in 56 nursing home residents.[22] Sixty-eight percent of the divalproex sodium patients (mean dose and blood level 826 mg and 45.4 mcg/ml, respectively) showed decreased agitation versus 52% of placebo patients. The most frequent side effects in the treated patients were sedation (39%) and nausea, vomiting, and diarrhea (25%). Regenold and Prasad reported on three cases of IV valproate sodium in geriatric patients.[23] Two of their cases were acutely manic, while the third was demented and agitated.[23] In each case, IV valproate sodium was associated with control of symptoms of agitation and was well-tolerated.[23]

The DSM-IV-TR diagnostic criteria for delirium specify that the patient exhibit a disturbance in consciousness, change in cognition or perceptual disturbance, symptom onset over a short period of time (e.g., hours to days) with diurnal fluctuations, and be attributable to the physiological consequences of a general medical condition.[24] In five of our six cases, these criteria were clearly met, based on clinical examination with longitudinal observation. All of these cases had substantial systemic disturbances that were temporally related to the development of the neuropsychiatric symptoms observed. In several of the cases reported in this study, there were coexisting psychiatric illnesses or histories of other psychiatric illnesses, but these other conditions were generally symptomatically stable and did not better account for the acute/subacute onset of symptoms than a diagnosis of delirium. The contribution of delirium to the clinical picture in Case 6 was more ambiguous, as the patient's chronic psychiatric illness and grossly paranoid behavior may have accounted for the bulk of his observed agitation. Nonetheless, we included his case in this series because of his variable LOC, multiple systemic disturbances, and to illustrate the challenges of delivering effective psychopharmacotherapy in an agitated NPO patient on a general medical service, where excess reliance on benzodiazepines may lead to excess sedation or other undesirable consequences.

In all of our cases, standard psychotropic medication regimens commonly used for the management of delirium and/or nonspecific agitation in the general hospital setting (antipsychotics and/or benzodiazepines) had initially been tried with limited success. Antipsychotics and/or benzodiazepines were continued while valproate was initiated. Therefore, the differential contributions of conventional antidelirium medications and valproate in the symptomatic improvement in these cases are difficult to assess definitively. It was our experience that patients' responses to conventional medications were inadequate in terms of symptom control and/or associated with concerning medication-related side effects. As such, the addition of valproic acid to existing regimens resulted in improved clinical response.

It could be argued that merely increasing the doses of antipsychotics and/or benzodiazepines may have resulted in similar symptom control. However, this approach was undertaken in each case with suboptimal results. In Case 4, the patient had a distant episode of likely EPS from oral haloperidol; IV haloperidol might be associated with a decrease of EPS and is a reasonable alternative. As our cases had been initially exposed to conventional therapy, it cannot be concluded from this limited series that valproate would necessarily be effective monotherapy for delirium. It is, however, reason-

able to suggest that valproic acid had a significant if not definitive adjunctive role in these cases.

In addition, it could be argued that recovery from delirium was due to correction of metabolic disturbances and management of systemic illnesses or that the episodes of delirium may have run their course with spontaneous reversal of symptoms. This point is also viable due to the multifactorial nature of delirium in most cases, which often makes it challenging to clearly attribute improvement to the effects of psychopharmacology, as intervention typically is concurrent with ongoing efforts at systemic stabilization. Unequivocal resolution of this matter would best be accomplished by large-scale, randomized, prospective trials of valproic acid versus conventional antidelirium medications in delirium cases.

The use of IV sodium valproate or PO valproic acid for treating delirium and/or agitation, as recommended by a CLS, is a logical expansion of the use of these drugs in treating psychiatric illnesses. They are especially attractive options when antipsychotics and/or benzodiazepines are ineffectual, require large and/or frequent dosing, or are saddled with concerning side effects. The IV form of valproate sodium (Depacon, Abbott Laboratories) may establish therapeutic serum levels and clinical efficacy more rapidly and can be easily converted to oral dosing when the patient is able to take oral medications. Close monitoring of serum drug levels and monitoring of liver-associated enzymes, bilirubin, platelet count, and amylase are advisable, especially in the critically ill patient. The liquid form of oral valproic acid (Depakene, Abbott Laboratories) can be used for delivery via NGT in a patient with a functioning gut for whom the theoretically more rapid onset of effect of the IV form is not essential.

Consultation-liaison psychiatrists are encouraged to expand their psychopharmacological armamentarium to include IV and PO valproate in their management of delirium.

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