Neonatal Lithium Measurement

Because neonatal blood samples are often collected in devices containing lithium heparin, unexpected lithium findings in neonates should be reconfirmed.

Two cases of neonatal blood sampling that appear to have lead to calculation of erroneous lithium levels were reported by physicians at the Motherisk Program in Canada. The newborns had been exposed to lithium before birth and both were breastfed by mothers who continued to receive lithium therapy. The first infant was found to have a baseline serum lithium level (at 20 hours after birth) of 4.19 mEq/L. Although this is a toxic concentration, the infant showed no symptoms of lithium toxicity. A follow-up measure on day 4 showed a concentration of 0.11 mEq/L and levels were undetectable thereafter. A second infant had undetectable lithium levels in the first few days after birth. The level was found to be 1.1 mEq/L on days 10 and 18, but because she showed no renal dysfunction or other signs of toxicity the sampling procedure was questioned. The use of lithium heparin-containing containers was suspected for both infants, but was documented only in the second case.


Lithium Levels and Bipolar Relapse

A pooled analysis of lithium maintenance trials found serum levels were associated with bipolar relapse state. Patients with higher levels were more likely to experience a depressive relapse.

**Methods:** Data from 2 randomized controlled trials comparing lithium, lamotrigine (*Lamictal*), or placebo maintenance in patients with bipolar I disorder were pooled. Patients (n=638) had been stabilized with randomized treatment and 167 continued lithium monotherapy for 18 months. The association between lithium levels (measured monthly) and polarity of relapse was investigated in 64 patients. The median serum level in the study population was 0.66 mEq/L. The levels above the median were considered high and those below the median were considered low.
Results: The relapse episode was depressive in 48 patients (75%) and hypomanic/manic or mixed in 16 patients (25%). Depressive episodes were preceded by increased lithium levels at the most recent monthly evaluation (mean increase above the median, 0.13 mEq/L; p<0.001). Relapse was depressive in all patients with a lithium level >0.75 mEq/L. Lithium dosages were numerically but not statistically greater in patients with depressive relapse. Duration of lithium therapy and bipolar state of the index episode did not appear to predict the relapse episode.

A comparison of patients with a depressive relapse showed 84% had high serum levels, compared with 57% having low levels (p=0.03). The odds ratio* for a depressive relapse (as opposed to manic or mixed) among the patients with high serum levels was 3.86.

Discussion: These results support using lower target lithium levels (0.4–0.8 mEq/L) for patients with bipolar disorder who are prone to depressive episodes and higher levels (0.6–1.0 mEq/L) for patients prone to manic or mixed episodes.

Severus W, Kleindienst N, Evoniuk G, Bowden C, et al: Is the polarity of relapse/recurrence in bipolar-I disorder patients related to serum lithium levels? Results from an empirical study. Journal of Affective Disorders. Published online December 3, 2008 at www.sciencedirect.com; doi 10.1016/j.jad.2008.10.009. From the University of Munich, Germany; and other institutions. The clinical studies from which the data were pooled were both funded by GlaxoSmithKline, and 1 author is employed by GlaxoSmithKline. No other sponsorship or commercial association was disclosed.

*Reference Guide Item.

Fluoxetine and Body Dysmorphic Disorder and Suicide

As many as 80% of patients with body dysmorphic disorder reportedly have a history of suicidal ideation and >25% have attempted suicide. SSRIs are the first-line treatment for these patients, but an increase in suicidal behavior in young SSRI-treated patients has been documented. A retrospective analysis of data from the only controlled trial of an SSRI in body dysmorphic disorder suggests fluoxetine protected some patients from worsening of suicidality.1

Methods: Adult outpatients with body dysmorphic disorder (n=67) received 12 weeks of randomized treatment with either fluoxetine (Prozac) or placebo.2 Those with clinically significant suicidal ideation and recent suicide attempts were excluded. This secondary analysis examined suicidality using specific items from the Hamilton Rating Scale for Depression.

Results: Suicidality emerged in 4 of 34 patients assigned to fluoxetine and in 6 of 33 patients assigned to placebo (12% vs 19%; p=ns). Suicidality worsened by study end in 6 placebo-treated patients, compared with none of the fluoxetine-treated patients (19% vs 0%; p=0.01). No patient attempted suicide during the study. Depressive symptoms improved to a significantly greater degree with fluoxetine, but there were no significant differences between the groups in other possible precursors to suicidality.

A subgroup analysis of 19 younger patients aged 18–24 years found suicidality emerged in 4 patients: 2 with fluoxetine and 2 with placebo (17% vs 29%; p=ns). A single patient in the placebo group experienced worsening suicidality.

Discussion: Fluoxetine appeared to have some protective effect against suicide, particularly among young adults. However, because patients under age 18 years were not studied, these results may not apply to younger populations.

1Phillips K, Kelly M: Suicidality in a placebo-controlled fluoxetine study of body dysmorphic disorder. International Clinical Psychopharmacology. Published online December 4, 2008 at www.intclipsychopharm.com; doi 10.1097/YIC.0b013e32831db2e9. From Brown University, Providence, RI. Funded by the NIMH.

First and Second Generation Differences

The comparative efficacy of antipsychotics has been widely debated. The newer second generation atypical agents are believed to be more effective for negative symptoms and to cause fewer extrapyramidal symptoms. A meta-analysis was undertaken to examine differences between the classes.

Methods: Double-blind randomized controlled trials comparing first and second generation antipsychotics in schizophrenia and related disorders were identified and 150 studies (>21,500 patients) were included in a meta-analysis. Haloperidol was the first generation comparator in 95 of the 150 studies and it was measured against oral formulations of amisulpride; aripiprazole; clozapine; olanzapine; quetiapine; risperidone; sertindole; ziprasidone; or zotepine. Efficacy was measured using the Positive and Negative Syndrome Scale or the Brief Psychiatric Rating Scale with response defined as a ≥50% reduction in score.

Results: Amisulpride, clozapine, olanzapine, and risperidone, but not the other atypicals, were significantly more effective than the first-generation agents at reducing overall symptoms (see table). Aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine were not more effective overall and did not produce significantly greater improvement in either positive or negative symptoms.

Relapse was reported in <10% of the studies, but olanzapine, risperidone, and sertindole had a significant advantage over first generation agents in relapse prevention. The other atypicals showed no significant advantage.

All of the second generation agents produced significantly fewer extrapyramidal symptoms than haloperidol. Among the atypicals, only aripiprazole and ziprasidone were not associated with significantly more weight gain than haloperidol. Clozapine, quetiapine, and zotepine were significantly more sedating than haloperidol.

Study Limitations: Because the vast majority of studies used the high-potency first generation agent haloperidol, these results cannot be extrapolated to all agents in the class. In addition, the small number of comparisons with medium-potency agents presents a possible bias.

Discussion: Although improved efficacy in terms of negative symptoms is generally attributed to the second generation agents as a class, this meta-analysis does not support that view. The agents that were most effective (i.e., amisulpride, clozapine, olanzapine, risperidone) were better in all domains including positive, negative, and overall symptoms. With the other atypicals, the effects on negative symptoms were larger than on positive symptoms, but the agents were not substantially better than haloperidol in controlling either symptom type.

Study Rating*—18 (100%): This study included all items necessary for a quality report.

Leucht S, Corves C, Arbter D, Engel R, et al: Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. Published online December 5, 2008 at www.thelancet.com; doi 10.1016/S0140-6736(08)61764-X. From Technische Universitat Munchen, Germany; and other institutions. Funded by the NIMH; and other sources.

Drug Trade Names: amisulpride (not available in the U.S.)—Deniban, Solian, Sulamid; aripiprazole—Abilify; clozapine—Clozaril; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal; sertindole (not available in the U.S.)—Serdolect; ziprasidone—Geodon; zotepine (not available in the U.S.)—Zoleptil

*Reference Guide Item.
Not Enough Clozapine Use?

The large NIMH Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which compared antipsychotics, allowed patients who discontinued a study drug to enter subsequent phases. The results of the 2 randomized trial phases have been previously published.\(^1\)\(^-\)\(^3\) In phase 3, patients who had stopped medication either for intolerance or non-response were treated with their physician’s choice of open-label monotherapy with oral aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone; depot fluphenazine; or combination therapy with any 2 treatment options. All agents were flexibly dosed and 270 patients were followed until they had received 18 months of treatment.\(^4\)

The study physicians rarely selected a first-generation agent (n=13 patients; \(<5\%\)). There were not significant differences in the number of patients receiving any of the other treatment options: aripiprazole (n=33); clozapine (n=37); combination (n=40); olanzapine (n=41); quetiapine (n=33); risperidone (n=36); ziprasidone (n=37). Treatment choices were based on clinical factors such as symptom severity and response to previous treatments. Aripiprazole and ziprasidone were chosen for patients with the highest body mass index. Patients for whom clozapine was chosen had a shorter duration of illness but relatively severe symptoms and were likely to have discontinued previous treatment for inadequate response. Symptoms improved in all groups with no significant differences, but changes were considered modest in patients with milder symptoms. Adverse effect profiles differed between the agents and few patients (7\%) stopped medication because of them.

This phase of the CATIE study provides additional information about the “real-world” use and effectiveness of antipsychotic agents in patients with chronic schizophrenia. The results suggest evidence-based guidelines that recommend clozapine for patients with poor response to previous treatments are not routinely followed.

4. Stroup T, Lieberman J, McEvoy J, Davis S, et al: Results of phase 3 of the CATIE schizophrenia trial. Schizophrenia Research. Published online November 20, 2008 at www.sciencedirect.com; doi 10.1016/j.schres.2008.10.011. From the University of North Carolina at Chapel Hill and other institutions. Funded by the NIMH. Several study authors disclosed receiving sponsorship or support from pharmaceutical industry sources.

Drug Trade Names: aripiprazole—Abilify; clozapine—Clozaril; fluphenazine, depot—Prolixin; olanzapine—Zyprexa; perphenazine—Trilafon; quetiapine—Seroquel; risperidone—Risperdal; ziprasidone—Geodon

Treating Mild-to-Moderate Mania

Both olanzapine and divalproex have been shown to be effective in the treatment of severe mania, but little research has focused on patients with milder symptoms. A multicenter randomized study found about 40\% of patients with mild-to-moderate manic or mixed symptoms responded to treatment with either agent.

Methods: Patients aged 18–65 years with bipolar disorder who were experiencing an acute manic or mixed episode without psychotic features were screened for study eligibility. Patients with a Young Mania Rating Scale (YMRS) score of 20–30 indicating mild-to-moderate symptoms were randomly assigned to double-blind treatment with 5–20 mg/day olanzapine (n=215), 500–2500 mg/day divalproex (n=201), or placebo (n=105) for 3 weeks. Because divalproex
required b.i.d. or t.i.d. dosing, all patients received study medications 3 times daily with placebo substituted for active drug after the total daily dose was administered. Acute treatment was followed by a 9-week double-blind extension phase during which those who had received placebo were switched to olanzapine and all others continued their assigned medication. The primary outcome measure was the YMRS with response defined as a ≥50% reduction in score and remission defined as a score of ≤12.

**Results:** After 3 weeks of treatment, YMRS scores were decreased from a baseline mean of 24 to 14 with olanzapine and to 16 with divalproex (p=ns). The groups also did not differ significantly in rates of response: 41% with olanzapine and 40% with divalproex; or remission: 43% and 40%, respectively.

At 12 weeks, YMRS improvements significantly favored olanzapine with a mean score of 10.5, compared with 13 in divalproex group (p=0.004). The response rate was also higher with olanzapine: 66% vs 57% with divalproex (p=0.04). However, a post-hoc analysis showed a large proportion of divalproex-treated patients had serum levels below the therapeutic range. Remission rates at 12 weeks were unchanged from the 3-week evaluation.

Adverse effects were consistent with the safety profiles for olanzapine and divalproex. Olanzapine produced more weight gain and somnolence than divalproex, which was in turn associated with more nausea, vomiting, and insomnia. Drop out rates were 26% at 3 weeks and 38% at 12 weeks with no significant differences in the rate or reasons for withdrawal between the treatment groups.

**Study Limitations:** Low serum divalproex concentrations may have affected treatment outcomes and the finding that more than half of patients had levels below the therapeutic range at 12 weeks may be an important factor contributing to the statistical superiority of olanzapine. In addition, the study had limited statistical power to detect differences between the active treatment groups.

**Study Rating**—17 (100%): This study included all items necessary for a quality randomized clinical trial report.


*Drug Trade Names*—**divalproex**—Depakene, Depakote; **olanzapine**—Zyprexa

*Reference Guide Item.

### Antidepressant-Associated Mania in Bipolar Depression

Pretreatment motor activation, pressured speech, and racing thoughts appear to be predictive of antidepressant-associated mania or hypomania.

**Methods:** The clinical correlates of treatment-emergent mania were studied in 176 outpatients participating in the Bipolar Collaborative Network. In addition to mood stabilizers or an antipsychotic, the participants had received adjunctive sertraline, venlafaxine, or bupropion. Treatment-emergent mania was defined as a Clinical Global Impression-Bipolar Disorder (CGI-BP) severity scale score of ≥4 (moderate) or a CGI Improvement rating of “much worse” or “very much worse.”

**Results:** Of the 176 patients, mania developed in 46 (26%). Patient age, age at onset, gender, personal and family history of bipolar disorder, presence of rapid cycling and/or comorbid disorders, and mood stabilizer treatments were not significantly different between patients who did and did not experience treatment-emergent mania. Although numerically low, the
pretreatment score on the Yale Mania Rating Scale (YMRS) motor activity item was more than 3 times higher in patients in whom mania developed, and the speech item score was at least twice as high. Scores for thought content were found to be 6–16 times higher in patients with treatment-emergent mania. This triad of YMRS items may be a surrogate marker for a mixed depressive state, which although not confirmed in DSM-IV is increasingly being recognized in clinical practice. Mixed depression differs from a full mixed episode because it occurs in the context of major depression rather than as a subtype of mania.


**Drug Trade Names**: bupropion—Wellbutrin; sertraline—Zoloft; venlafaxine—Effexor

### Antiepileptic Suicide Warning

The FDA has issued an advisory about the increased risk for suicidality in patients treated with antiepileptics for epilepsy, psychiatric disorders, migraine headaches, and other conditions. Although they have not required a Boxed Warning, the labeling for all antiepileptics will be updated and medication guides detailing the risk will be created. The background for the advisory is in a *Psychiatry Drug Alerts* report published in March 2008 and reprinted below.

**FDA News**: FDA requires warnings about risk of suicidal thoughts and behavior for antiepileptic medications. Available at: www.fda.gov/bbs/topics/NEWS/NEW01927.html.

#### Antiepileptic Warning

Risk for suicidality appears to be increased 2-fold in patients treated with an antiepileptic agent, compared with placebo. The absolute risk is small.

After a preliminary analysis suggested increased risk for emergent suicidality with several antiepileptics, the FDA reviewed data from 199 placebo-controlled trials with designs that allowed for investigation of suicidality. The drugs included in these studies were: carbamazepine; felbamate; gabapentin; lamotrigine; levetiracetam; oxcarbazepine; pregabalin; tiagabine; topiramate; valproate; and zonisamide. Although other antiepileptics are marketed, evaluable data were available only for these agents. The FDA expects the increased risk to extend to all drugs in the class.

The 199 trials included >43,000 patients aged ≥5 years and examined pharmacotherapy for epilepsy, psychiatric illnesses, and pain syndromes. The absolute risk for suicide with antiepileptics was small; 4 of the nearly 28,000 antiepileptic-treated patients committed suicide, compared with none receiving placebo. However, relative to placebo the risk for suicidal behavior or suicidal ideation was nearly doubled in treated patients (0.43% vs 0.22%). Increased risk emerged as early as 1 week after starting treatment and continued through 24 weeks (the longest trial duration). There was no significant difference in risk between the agents and no subgroup of patients appeared to account for the increase. Relative risk was higher among patients with epilepsy than those treated for psychiatric or other conditions.

Patients taking antiepileptic drugs should be carefully monitored for behavioral changes that could be precursors to emerging suicidality including anxiety, agitation, hostility, and mania or hypomania. Although a causal relationship has not been established, the FDA anticipates the addition of a class warning to the labeling for all antiepileptic drugs.

**FDA Alert**: Information for healthcare professionals suicidality and antiepileptic drugs. Available at www.fda.gov/ceder/drug/InfoSheets/HCP/antiepilepticsHCP.htm.

**Drug Trade Names**: carbamazepine—Epitol, Tegretol; felbamate—Felbatol; gabapentin—Neurontin; lamotrigine—Lamictal; levetiracetam—Keppra; oxcarbazepine—Trileptal; pregabalin—Lyrica; tiagabine—Gabitril; topiramate—Topamax; valproate—Depakene, Depakote, Depacon; zonisamide—Zonegran
Phenytoin Rash and Genetics

Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are known to occur in a small proportion of patients treated with carbamazepine, oxcarbazepine, lamotrigine, and other anticonvulsants. A 2007 FDAMed Watch Alert warned that the reaction is significantly more common in carbamazepine-treated patients with the HLA-B*1502 human leukocyte antigen allele. This allele is present almost exclusively in people of Asian descent. Preliminary data now suggests risk for SJS and TEN may also be significantly increased in patients with the allele who are treated with phenytoin or phosphenytoin.


FDA Alert: Information for healthcare professionals phenytoin (marketed as Dilantin, Phenytek and generics) and fosphenytoin sodium (marketed as Cerebyx and generics). Available at www.fda.gov/cder/drug/InfoSheets/HCP/phenytoin_fosphenytoinHCP.htm.

Drug Trade Names: carbamazepine—Epitol, Tegretol; lamotrigine—Lamictal; oxcarbazepine—Trileptal; phenytoin—Dilantin; phosphenytoin—Cerebyx

Varenicline Improved Ataxia

Movement and speech disturbances associated with spinocerebellar ataxia, an inherited neurodegenerative disorder, markedly improved with varenicline (Chantix) treatment in 2 patients.

A 63-year-old woman presented to a movement disorders clinic for management of spinocerebellar ataxia. Her symptoms included poor balance, gait dysfunction, speech disturbance, postural tremor, dystonia, and akinesia and she was unable to walk independently. She had a long history of cigarette smoking and was started on varenicline for smoking cessation. Although she did not stop smoking, within 10 days of varenicline initiation she reported better ambulatory stability and easier walking. After 1 month, the gait dysfunction, akinesia, and other symptoms were markedly improved and she was able to walk without a cane or walker.

The second patient, a 51-year-old woman, had similar symptoms attributed to spinocerebellar ataxia, but was not a smoker. She was also treated with varenicline off-label and within 3 weeks experienced marked improvement in balance, walking ability, speech, and other symptoms. She discontinued varenicline for financial reasons and the neurologic symptoms returned to pretreatment levels within 4 weeks.

It is unclear how varenicline produced these improvements. The agent is a highly selective partial agonist for nicotinic acetylcholine receptors, which have been suggested to modulate cerebellar activity. Studies have examined antianxiolytics, antidepressants, and anticonvulsants in ataxia, but results have been conflicting and efficacy was limited. Because there are no confirmed effective treatments for ataxia, controlled studies of varenicline appear to be warranted.


Aripiprazole After NMS

A 42-year-old female with schizoaffective disorder bipolar type had a history of neuroleptic malignant syndrome associated with fluphenazine. Symptoms resolved after fluphenazine was stopped, but subsequent treatment trials with risperidone and olanzapine produced rapid elevations in creatine phosphokinase (CPK) suggestive of NMS. She received maintenance therapy with extended-release valproic acid, topiramate, and duloxetine for about 1 year before presenting with increasing confusion, paranoid ideation, and auditory hallucinations. On admission, 25 mg/day quetiapine, 40 mg/day ziprasidone, and 0.5 mg lorazepam b.i.d. were
added to her outpatient medication regimen. Because of the previous NMS, her CPK level was checked daily and it steadily increased to >2100 U/L (normal range, 40–325 U/L) on day 9. Ziprasidone and quetiapine were stopped and CPK quickly declined. She underwent 12 ECT sessions and the psychosis and agitation improved. Valproic acid and topiramate were discontinued and she received long-term maintenance with 10 mg/day aripiprazole. Duloxetine and ECT were continued. CPK levels were routinely monitored and have remained within the normal range for 6 months.

**Discussion:** Dopamine receptor blockade is believed to underlie NMS. Because aripiprazole is a partial dopamine agonist it may be an alternative for patients with a history of NMS. It is also possible that aripiprazole was tolerated because the course of ECT produced brain changes that altered the patient’s susceptibility to NMS.


**Drug Trade Names:**
- aripiprazole—*Abilify*;
- duloxetine—*Cymbalta*;
- fluphenazine—*Prolixin*;
- lorazepam—*Ativan*;
- olanzapine—*Zyprexa*;
- quetiapine—*Seroquel*;
- risperidone—*Risperdal*;
- topiramate—*Topamax*;
- valproic acid, extended-release—*Depakote ER*;
- ziprasidone—*Geodon*