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Medication Effects and Interactions

The following drugs were reviewed, using one or more online drug information databases (e.g., RxList, Drugs.com, DrugDigest.org., PDR Online, etc.) They were identified as current active medications.

zolpidem (Ambien), mometasone (Asmanex), aspirin, ipratropium (Atrovent), calcium carbonate, clonazepam, divalproex sodium (Depakote), estradiol, magnesium, esomeprazole (Nexium), progesterone, selenium, cyanocobalamin (Vitamin B-12), vitamin E, sertraline (Zoloft)

Interactions between selected drugs

Aspirin and calcium carbonate (Moderate Drug-Drug). **MONITOR:** Chronic administration of antacids may reduce serum salicylate concentrations in patients receiving large doses of aspirin or other salicylates. The mechanism involves reduction in salicylate renal tubular reabsorption due to urinary alkalization by antacids, resulting in increased renal salicylate clearance. In three children treated with large doses of aspirin for rheumatic fever, serum salicylate levels declined 30% to 70% during coadministration with a magnesium and aluminum hydroxide antacid. Other studies have found similar, albeit less dramatic results. Antacids reportedly have no effect on the oral bioavailability of aspirin in healthy adults. However, administration of antacids containing either aluminum and magnesium hydroxide or calcium carbonate two hours before aspirin dosing led to reduced absorption of aspirin in uremic patients.

MANAGEMENT: Patients treated chronically with antacids (or oral medications that contain antacids such as didanosine buffered tablets or pediatric oral solution) and large doses of salicylates (i.e. 3 g/day or more) should be monitored for potentially diminished or inadequate analgesic and anti-inflammatory effects, and the salicylate dosage adjusted if necessary.

Aspirin and sertraline (Moderate Drug-Drug). **MONITOR:** Serotonin reuptake inhibitors (SRIs) may potentiate the risk of bleeding in patients treated with agents that affect hemostasis such as anticoagulants, platelet inhibitors, thrombin inhibitors, thrombolytic agents, or agents that commonly cause thrombocytopenia. The tricyclic antidepressant, clomipramine, is also a strong SRI and may interact similarly. Serotonin release by platelets plays an important role in hemostasis, thus SRIs may alter platelet function and induce bleeding. Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic agents that interfere with serotonin reuptake. Additional epidemiological studies have confirmed the association between use of these agents and the occurrence of upper gastrointestinal bleeding, and concurrent use of NSAIDs or aspirin was found to potentiate the risk. Preliminary data also suggest that there may be a pharmacodynamic interaction between SSRIs and oral anticoagulants that can cause an increased bleeding diathesis. Concomitant administration of paroxetine and warfarin, specifically, has been associated with an increased frequency of bleeding without apparent changes in the disposition of either drug or changes in the prothrombin time. Bleeding has also been reported with fluoxetine and warfarin, while citalopram and sertraline have been reported to prolong the prothrombin time of patients taking warfarin by about 5% to 8%.

MANAGEMENT: Caution is advised if SRIs or clomipramine are used in combination with other drugs that affect hemostasis. Close clinical and laboratory observation for hematologic complications is recommended. Patients should be advised to promptly report any signs of bleeding to their physician, including pain, swelling, headache, dizziness, weakness, prolonged bleeding from cuts, increased menstrual flow, vaginal bleeding, nosebleeds, bleeding of gums from brushing, unusual bleeding or bruising, red or brown urine, or red or black stools.

Aspirin and divalproex sodium (Moderate Drug-Drug). **MONITOR:** Salicylates, particularly aspirin, may displace valproate from protein binding sites and inhibit its clearance. Four-fold increases in the free fraction of valproate have

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been reported in children. Increased therapeutic and toxic effects may be expected to occur. This interaction is more likely with large or prolonged doses of salicylates.

MANAGEMENT: Small single doses of salicylates are unlikely to cause significant effects. However, patients who take large doses of salicylates or over a prolonged period of time should be closely monitored for clinical and laboratory evidence of valproate toxicity and hepatotoxicity. Free fraction of valproate may be particularly helpful in detecting this interaction. Patients should be advised to notify their physician if they experience possible symptoms of toxicity (e.g., malaise, weakness, lethargy, drowsiness, nausea, vomiting, or abdominal pain).

! **clonazepam and sertraline** (Moderate Drug-Drug). **MONITOR:** Central nervous system- and/or respiratory-depressant effects may be additively or synergistically increased in patients taking multiple drugs that cause these effects, especially in elderly or debilitated patients.

MANAGEMENT: During concomitant use of these drugs, patients should be monitored for potentially excessive or prolonged CNS and respiratory depression. Ambulatory patients should be counseled to avoid hazardous activities requiring complete mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.

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! **clonazepam and divalproex sodium** (Moderate Drug-Drug). **MONITOR:** A single study has suggested that combination therapy with clonazepam and valproic acid may cause severe drowsiness and decreased seizure control. Other studies have not supported this finding. Several case reports have suggested that the combination of clonazepam and valproic acid may precipitate absence status; however, this combination has had beneficial effects in the treatment refractory absence seizures. The mechanism and causality have not been determined.

MANAGEMENT: Monitoring for altered efficacy and safety is recommended if valproic acid (or its derivatives) and clonazepam are used together. Alternative therapy may be appropriate if significant side effects or loss of seizure control occur.

! **estradiol and divalproex sodium** (Moderate Drug-Drug). **MONITOR:** A case report suggests that estrogens or progestins may decrease the serum concentrations and pharmacologic effects of valproic acid (VPA). The proposed mechanism is induction of hepatic glucuronidation by sex hormones. The case report involves a 26-year-old woman with a history of epilepsy since childhood. Petite mal seizures developed at age seven, which were treated with ethosuximide for approximately 2 years. She was seizure-free from age nine and did not require medication until age 13, when she had her first generalized convulsive seizure that corresponded with her first menstrual cycle. She continued to have one or two episodes each year under treatment with a variety of anticonvulsants, but had her last generalized convulsion at age 23 while taking VPA. Subsequently, she developed partial seizures that began around the time she was started on an oral contraceptive containing ethynodiol 1 mg and ethinyl estradiol 35 mcg. The patient's seizure charting indicated that her partial seizures occurred more frequently during the weeks she was taking active contraceptive pills than the weeks when she took the inactive pills. Specifically, over a 5-month period, she had 12 seizures during 105 days of active pill use and none during 35 days of inactive pill use. In two separate cycles, morning trough serum VPA level during the third week of active pill use was 39% and 64% of that between days 5 and 7 of inactive pill use. Conversely, VPA reportedly has no effects on the pharmacokinetics of contraceptive steroids. In one study, VPA given at a dosage of 200 mg twice daily for 2 months did not significantly affect the systemic exposure (AUC) of ethinyl estradiol or levonorgestrel in six women.

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MANAGEMENT: Pharmacologic response and serum valproic levels should be monitored more closely whenever estrogen- and/or progestin-containing drugs are added to or withdrawn from therapy, and the valproic acid dosage adjusted as necessary. Patients should be advised to contact their physician if they experience loss of seizure control or symptoms of valproic acid toxicity such as tremors, ataxia, nystagmus, increased seizures, and changes in mental status. In patients receiving oral contraceptives, gradual transient increases in valproic acid levels will likely occur during the pill-free week for women not also taking an enzyme-inducing drug (e.g., carbamazepine, phenytoin, phenobarbital, primidone, rifampin). The increase in valproic acid levels will be greater if the dose of valproic acid is increased in the few days before or during the pill-free week.

! progesterone and divalproex sodium (Moderate Drug-Drug). **MONITOR:** A case report suggests that estrogens or progestins may decrease the serum concentrations and pharmacologic effects of valproic acid (VPA). The proposed mechanism is induction of hepatic glucuronidation by sex hormones. The case report involves a 26-year-old woman with a history of epilepsy since childhood. Petite mal seizures developed at age seven, which were treated with ethosuximide for approximately 2 years. She was seizure-free from age nine and did not require medication until age 13, when she had her first generalized convulsive seizure that corresponded with her first menstrual cycle. She continued to have one or two episodes each year under treatment with a variety of anticonvulsants, but had her last generalized convulsion at age 23 while taking VPA. Subsequently, she developed partial seizures that began around the time she was started on an oral contraceptive containing ethynodiol 1 mg and ethinyl estradiol 35 mcg. The patient's seizure charting indicated that her partial seizures occurred more frequently during the weeks she was taking active contraceptive pills than the weeks when she took the inactive pills. Specifically, over a 5-month period, she had 12 seizures during 105 days of active pill use and none during 35 days of inactive pill use. In two separate cycles, morning trough serum VPA level during the third week of active pill use was 39% and 64% of that between days 5 and 7 of inactive pill use. Conversely, VPA reportedly has no effects on the pharmacokinetics of contraceptive steroids. In one study, VPA given at a dosage of 200 mg twice daily for 2 months did not significantly affect the systemic exposure (AUC) of ethinyl estradiol or levonorgestrel in six women.

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! sertraline and zolpidem (Moderate Drug-Drug). **MONITOR:** Central nervous system- and/or respiratory-depressant effects may be additively or synergistically increased in patients taking multiple drugs that cause these effects, especially in elderly or debilitated patients.

MANAGEMENT: During concomitant use of these drugs, patients should be monitored for potentially excessive or prolonged CNS and respiratory depression. Ambulatory patients should be counseled to avoid hazardous activities requiring complete mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.

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MANAGEMENT: During concomitant use of these drugs, patients should be monitored for potentially excessive or prolonged CNS and respiratory depression. Ambulatory patients should be counseled to avoid hazardous activities requiring complete mental alertness and motor coordination until they know how these agents affect them, and to notify their physician if they experience excessive or prolonged CNS effects that interfere with their normal activities.

Calcium carbonate and divalproex sodium (Minor Drug-Drug). Limited data suggest that concurrent administration of antacids may increase the bioavailability of valproic acid. The mechanism of interaction is unknown. In seven healthy volunteers, coadministration of a single 500 mg dose of valproic acid one hour after breakfast and an antacid containing aluminum-magnesium hydroxide (dose equal to 160 mEq of neutralizing capacity) one and three hours after meals and at bedtime on the same day resulted in a mean 12% increase (range 3% to 28%) in the total area under the concentration-time curve (AUC) of valproic acid compared to administration alone. These changes are unlikely to be of clinical importance, and no special precautions appear to be necessary. Equivalent doses of antacids containing either aluminum hydroxide-magnesium trisilicate or calcium carbonate also increased the AUC of valproic acid, but the differences were not statistically significant.

Aspirin and esomeprazole (Minor Drug-Drug). Coadministration with proton pump inhibitors may decrease the oral bioavailability of aspirin and other salicylates. The interaction has been studied with omeprazole and aspirin, although data are conflicting. In one study, pretreatment with omeprazole (20 mg/day for 2 days) in 11 healthy volunteers led to a significant and progressively greater reduction in the mean serum salicylate level at 30, 60, and 90 minutes after administration of aspirin (650 mg single dose). The investigators suggest that acid suppression may reduce the lipophilic nature of aspirin, thereby adversely affecting its absorption from the gastrointestinal tract. Another study found no effect of omeprazole pretreatment (20 mg/day for 4 days) on plasma salicylate and aspirin levels, skin bleeding times, or antiplatelet effect of low-dose aspirin (125 mg single dose) in 14 healthy volunteers. However, these results do not exclude the possibility that omeprazole might interfere with the analgesic, antipyretic, or anti-inflammatory effects of aspirin, which has been demonstrated in rats.

Proton pump inhibitors may enhance the release rate of salicylates from enteric-coated formulations due to premature disruption of the coating and intragastric release of the drug secondary to an increase in gastric pH. In eight healthy volunteers, omeprazole pretreatment (20 mg/day for 4 days) did not affect the bioavailability of salicylate from uncoated aspirin tablets but significantly increased the absorption rate of salicylate from enteric-coated sodium salicylate tablets. The clinical significance of this interaction is unknown. Theoretically, it may increase the risk of gastric adverse effects associated with salicylates.

Clonazepam and calcium carbonate (Minor Drug-Drug). A number of studies have reported that antacids can delay the gastrointestinal absorption and reduce the peak plasma concentration (C_{max}) of some benzodiazepines, including clorazepate, chlordiazepoxide and diazepam, although the overall extent of absorption is generally not affected. The exact mechanism of interaction is unknown but may involve delayed gastric emptying or cation binding of the benzodiazepine. As a result, benzodiazepine onset of action may be delayed and clinical effects diminished. However, one study reported a significant increase in diazepam absorption during coadministration with aluminum hydroxide, and there was a marginal increase in the onset of sedative effect. Aluminum hydroxide also increased the C_{max} and systemic exposure (AUC) of triazolam in 11 dialysis patients such that their drug levels reached into the range observed for the matched controls. In contrast, another study by the same group of investigators found no significant effect of aluminum hydroxide on temazepam absorption or C_{max} in 11 patients with end-stage renal disease. A multi-dose study also failed to find an effect of antacids on the steady-state levels of N-desmethyldiazepam, the active metabolite of clorazepate, although an acidic environment is thought to be necessary for the rapid conversion. Based on available data, the clinical significance of this interaction appears to be minor. As a precaution, patients may want to consider separating the administration times of benzodiazepines and antacids or oral medications that contain antacids (e.g., didanosine buffered tablets or pediatric oral solution) by 2 to 3 hours.

Cyanocobalamin and esomeprazole (Minor Drug-Drug). By reducing or suppressing gastric acid secretion, H₂-receptor antagonists and proton pump inhibitors may interfere with the gastrointestinal absorption of vitamin B12, a process that is dependent on the presence of gastric acid and pepsin. Clinical studies have shown that dietary (i.e., protein-bound) vitamin B12 malabsorption can occur during treatment with these agents, particularly the proton pump inhibitors, although the likelihood of developing clinically significant deficiency over time is unknown. There has been one reported case of vitamin B12 deficiency with megaloblastic anemia in a patient who received omeprazole at a

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minimum of 40 mg/day for 4 years. Also uncertain is whether acid reduction or suppression can affect the absorption of vitamin B12 ingested in the form of oral supplements such as cyanocobalamin and mecobalamin. Parenteral or intranasal administration is generally the preferred route in the treatment of B12 deficiency-related anemia.

divalproex sodium and esomeprazole (Minor Drug-Drug). The coadministration of esomeprazole and drugs that are substrates of the CYP450 2C19 enzymatic pathway may result in elevated plasma concentrations of those drugs. The mechanism is decreased clearance due to competitive inhibition of CYP450 2C19 activity by esomeprazole. The clinical significance of this potential interaction, if any, is unknown. Caution is advised if esomeprazole is used concomitantly with medications that undergo metabolism by CYP450 2C19, particularly those with a narrow therapeutic range.

Interactions between selected drugs and food

clonazepam (Moderate Drug-Food). **MONITOR:** Grapefruit juice may increase the plasma concentrations of some orally administered drugs that are substrates of the CYP450 3A4 isoenzyme. The proposed mechanism is inhibition of CYP450 3A4-mediated first-pass metabolism in the gut wall by certain compounds present in grapefruits. The extent and clinical significance are unknown. Moreover, pharmacokinetic alterations associated with interactions involving grapefruit juice are often subject to a high degree of interpatient variability.

MANAGEMENT: Patients who regularly consume grapefruits and grapefruit juice should be monitored for adverse effects and altered plasma concentrations of drugs that are metabolized by CYP450 3A4. Grapefruits and grapefruit juice should be avoided if an interaction is suspected. Orange juice is not expected to interact with these drugs.

progesterone (Moderate Drug-Food). **MONITOR:** Grapefruit juice may increase the plasma concentrations of some orally administered drugs that are substrates of the CYP450 3A4 isoenzyme. The proposed mechanism is inhibition of CYP450 3A4-mediated first-pass metabolism in the gut wall by certain compounds present in grapefruits. The extent and clinical significance are unknown. Moreover, pharmacokinetic alterations associated with interactions involving grapefruit juice are often subject to a high degree of interpatient variability.

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sertraline (Moderate Drug-Food). **MONITOR:** Grapefruit juice may increase the plasma concentrations of some orally administered drugs that are substrates of the CYP450 3A4 isoenzyme. The proposed mechanism is inhibition of CYP450 3A4-mediated first-pass metabolism in the gut wall by certain compounds present in grapefruits. The extent and clinical significance are unknown. Moreover, pharmacokinetic alterations associated with interactions involving grapefruit juice are often subject to a high degree of interpatient variability.

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zolpidem (Moderate Drug-Food). **ADJUST DOSING INTERVAL:** Administration of zolpidem with food may delay the onset of hypnotic effects. In 30 healthy subjects, administration of zolpidem 20 minutes after a meal resulted in decreased mean peak plasma drug concentration (C_{max}) and area under the concentration-time curve (AUC) by 25% and 15%, respectively, compared to fasting. The time to reach peak plasma drug concentration (T_{max}) was prolonged by 60%, from 1.4 to 2.2 hours.

MANAGEMENT: For faster sleep onset, zolpidem should not be administered with or immediately after a meal.

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Esomeprazole (Moderate Drug-Food). **ADJUST DOSING INTERVAL:** Food may interfere with the absorption of esomeprazole. The manufacturer reports that the area under the concentration-time curve for esomeprazole following a single 40 mg dose was 33% to 53% lower when administered after food intake as opposed to during fasting conditions.

MANAGEMENT: Esomeprazole should be taken at least one hour before meals.

Estradiol (Minor Drug-Food). The coadministration with grapefruit juice may increase the bioavailability of oral estrogens. The proposed mechanism is inhibition of CYP450 3A4-mediated first-pass metabolism in the gut wall induced by certain compounds present in grapefruits. In a small, randomized, crossover study, the administration of ethinyl estradiol with grapefruit juice (compared to herbal tea) increased peak plasma drug concentration (Cmax) by 37% and area under the concentration-time curve (AUC) by 28%. Based on these findings, grapefruit juice is unlikely to affect the overall safety profile of ethinyl estradiol. However, as with other drug interactions involving grapefruit juice, the pharmacokinetic alterations are subject to a high degree of interpatient variability. Also, the effect on other estrogens has not been studied.

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Adverse effect analysis

The goal was to identify medications whose side effects included myoclonus or respiratory problems. *This type of review is not individualized, and is subject to overinterpretation. Side effects reported for medications tend to be overinclusive, since rare, idiosyncratic or even unconfirmed reports are often represented in the literature alongside well known effects. To be clinically useful, a report of this type must be reviewed carefully by a professional familiar with the pharmacology of each drug in question, as well as the particular circumstances of the case at hand.*

Potentially Relevant Reported Side Effects of Selected Drugs

zolpidem (Ambien)	Reported have been: palpitations; nausea, dyspepsia, diarrhea, abdominal pain, constipation, anorexia and vomiting; neuropathy, tetany, yawning, shortness of breath. Hiccups have been reported occurring in greater than 1% of subjects.
mometasone (Asmanex)	Reported have been: dyspepsia, abdominal pain, nausea, flatulence, gastroenteritis, vomiting, anorexia; dysphonia.
aspirin	Reported have been tinnitus , nausea; dyspepsia; heartburn.

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ipratropium (Atrovent)	Reported have been: nausea, gastrointestinal distress, vomiting, palpitations, muscular tremor, hoarseness, laryngospasm, bronchospasm.
clonazepam	Reported have been: aphonia, choreiform movements, respiratory depression, tremor, shortness of breath, palpitations, anorexia, constipation, diarrhea, encopresis, gastritis, increased appetite, nausea, abdominal pain, ataxia, dysarthria, hoarseness, twitching , hypertonia.
divalproex sodium (Depakote)	Reported have been: dyspepsia, nausea, vomiting, diarrhea, abdominal pain, hypertonia, tremor, tinnitus, twitching, hiccups .
estradiol	Reported have been: chorea, nausea; vomiting; abdominal cramps; bloating; colitis; diarrhea; dyspepsia; flatulence; gastritis; gastroenteritis.
esomeprazole (Nexium)	Reported have been: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, hiccup, hypertonia, tremor.
progesterone	Reported have been: palpitations, dyspnea, hypertonia, tremor, tinnitus, constipation, nausea, abdominal pain, abdominal distention, diarrhea, vomiting, dyspepsia, flatulence, gastritis, gastroenteritis, anorexia.
sertraline (Zoloft)	Reported have been: weight loss , abdominal pain, anorexia, constipation, diarrhea, dyspepsia , nausea, tremor, palpitations, tinnitus, hypertonia, twitching, hyperkinesia, dysphonia.

Summary

It is not possible to draw definite conclusions about the possibility of a **drug effect** contributing to your condition. However, adverse effects of medications may cause or complicate many symptoms, and always need to be considered. Numerous factors must be weighed, in analyzing the potential significance of reported reactions to a given case, including dose, timing, concomitant medications, age, sex, health status, and others. The reported effects of some of these medications suggest that it may be valuable to share a copy of this list with your clinicians. As always, the patient’s attending physicians have the most immediate information about whether any of the following information may be relevant to the case.