

# Online video games pose addiction risk for kids

Treatment is available, but many gamers are in denial that their behaviour is unhealthy

by Lisa Darwen

MONTREAL | All around the world, more and more kids are becoming online video game addicts.

While most parents would rather their kids play video games instead of picking up other bad habits like smoking, some think spending 10 to 15 hours a day in front of a computer is not healthy and are seeking help for their kids.

For the past two years, Montreal psychologist Jean-Pierre Rochon has been treating up to 10 kids a year between the ages of 12 and 25 that have serious video game addictions. One-third of the patients seek help on their own accord but most are in denial that what they're doing is unhealthy.

Rochon said that like most

addicts, gamers use their behaviour to avoid something. He works with the kids' feelings to try and unveil what it is they're avoiding so he can work with them on the real issues that are bothering them.

Rochon noted that war and role-playing games tend to be the most addictive because the player has to stay in their role from day to day or they'll regress in the game.

## Dangers underestimated

If the gamers are in denial, they tend to underestimate the dangers of their addiction: low self-esteem, depression, failing school, not eating and losing friends.

China, which has the second largest online population behind the U.S., has opened its first official Internet addiction clinic. It



Kids may become addicted to video games to avoid other problems.

treats obsessed Internet gamers by integrating social sports such as basketball and playing cards into their lives. The patients also

receive medication, acupuncture and shock therapy where nerve impulses are stimulated by 30-volt charges to pressure points.

Table 3: Drug Interactions (cont'd)

Agents	Observed Interactions
NSAIDs	The short-term concomitant administration of PLAVIX and naproxen increased occult gastrointestinal blood loss, in a clinical study conducted in healthy volunteers. Consequently, there is a potential increased risk of gastrointestinal bleeding (See <b>WARNINGS</b> ).
Heparin	Clopidogrel at steady state did not modify the effect of heparin on coagulation in a clinical study conducted in healthy volunteers. Coadministration of heparin had no effect on platelet aggregation inhibition induced by PLAVIX.
Warfarin	Because of the increased risk of bleeding the concomitant administration of warfarin with clopidogrel should be undertaken with caution (See <b>WARNINGS</b> ).
Digoxin, Theophylline, Antacids	There was no modification of the pharmacokinetics of digoxin or theophylline with the coadministration of PLAVIX at steady state. Antacids did not modify the extent of PLAVIX absorption.
Other	No clinically significant pharmacodynamic interactions were observed when clopidogrel was coadministered in clinical studies to investigate drug interaction with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of PLAVIX was slightly enhanced by the coadministration of phenobarbital; however, this was not considered to be clinically significant. Pharmacodynamic activity of PLAVIX was not changed with the coadministration of cimetidine. Pharmacodynamic activity of PLAVIX was not significantly influenced by the coadministration of estrogen.

Clinically significant adverse interactions were not detected in the CAPRIE and/or CURE studies where patients received a variety of concomitant medications including ASA, diuretics, beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, lipid-lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, hormone replacement therapy, unfractionated and/or LMW heparin, and glycoprotein IIb/IIIa inhibitors. A review of the clinical trial data indicates that there is no evidence of an interaction between PLAVIX and atorvastatin. In CAPRIE, patients on HMG CoA reductase inhibitors and clopidogrel experienced a higher incidence of bleeding events (primarily epistaxis). Patients on HMG CoA reductase inhibitors and ASA experienced a higher incidence of intracranial hemorrhage. There is no known pathophysiological or pharmacological explanation for these observations.

At high concentrations *in vitro*, clopidogrel inhibits isoenzyme CYP 2C9 of the cytochrome P450 system. Accordingly, PLAVIX may interfere with the metabolism of drugs such as phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many non-steroidal anti-inflammatory agents. There are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with PLAVIX.

**Laboratory Test Interactions:** None known.

## ADVERSE REACTIONS

PLAVIX (clopidogrel bisulfate) has been evaluated for safety in more than 17,500 patients, including over 9,000 patients treated for 1 year or more.

## CAPRIE:

PLAVIX was well tolerated compared to ASA in CAPRIE. With few exceptions, the overall tolerability of PLAVIX was similar regardless of age, sex and race. However, in women there was a slightly higher incidence of bleeding disorders in the clopidogrel group (11.36% vs 9.88%).

**Clinically Important Adverse Events** The clinically important adverse events observed in CAPRIE were the following:  
**Neutropenia and thrombocytopenia:** Although these events were observed, PLAVIX was not associated with an increase in the incidence of neutropenia or thrombocytopenia.

**Granulocytopenia:** Granulocytopenia (<1,200/mm<sup>3</sup>) occurred in 8 patients taking PLAVIX and 14 patients taking ASA. Among those, severe granulocytopenia (<450/mm<sup>3</sup>) was observed in 4 patients (0.04%) that received PLAVIX and 2 patients (0.02%) that received ASA. Two of the 9,599 patients who received PLAVIX had neutrophil counts of zero. None of the 9,586 patients who received ASA had neutrophil counts of zero. Although the risk of myelotoxicity with clopidogrel appears to be quite low, this possibility should be considered when a patient receiving clopidogrel demonstrates fever or other signs of infection.

One case of aplastic anemia occurred on clopidogrel treatment.  
**Bleeding and clotting disorders:** One case of Hensch-Schonlein purpura (acute visceral symptoms: vomiting, diarrhea, abdominal distention, hematuria, renal colic) was reported in a patient taking PLAVIX. The patient recovered without sequelae within one month. Rare cases of platelet count  $\leq 30,000/\text{mm}^3$  have been reported.

**Skin disorders:** There was no notable difference between treatment groups in the incidence of bullous eruptions (0.23% PLAVIX vs 0.16% ASA). One case of a severe bullous eruption was reported in a patient taking PLAVIX.

**Hepatic and biliary disorders:** The overall incidence of hepatic and biliary disorders was similar in patients treated with clopidogrel (3.5%) compared to ASA (3.4%). The most frequent events were increased liver enzymes and bilirubinemia.

Table 4: Patients Discontinued Because of Adverse Experiences in CAPRIE (Number and Percentage of Patients)

Adverse Experience	Study drug permanently discontinued	
	PLAVIX	ASA
Rash	86 (0.90%)	39 (0.41%)*
Diarrhea	40 (0.42%)	26 (0.27%)
Indigestion/nausea/vomiting	182 (1.90%)	231 (2.41%)*
Any bleeding disorder	115 (1.20%)	131 (1.37%)
Intracranial hemorrhage	20 (0.21%)	32 (0.33%)
Gastrointestinal hemorrhage	50 (0.52%)	89 (0.93%)*
Abnormal liver function	22 (0.23%)	28 (0.29%)

\* Statistically significant,  $p < 0.05$

A summary of the clinically relevant adverse effects observed in CAPRIE are presented in the table below. In CAPRIE, patients with a known intolerance to ASA were excluded from the study.

Table 5: Summary of Adverse Events - CAPRIE Trial

Adverse Event	PLAVIX % Incidence (N=9599)	ASA % Incidence (N=9586)
Hemorrhages or bleeding disorders:		
- intracranial hemorrhage	0.4	0.5
- gastrointestinal bleeding	2.0	2.7*
- requiring hospitalization	0.7	1.1
- purpura (primarily bruising and ecchymosis)	5.3*	3.7
- epistaxis	2.9	2.5
- eye bleeding	0.8	0.5
- conjunctival†	0.3	0.2
- with sequelae‡	0.1	0.1
Platelet disorders:		
- severe thrombocytopenia ( $0 \leq x < 80,000/\text{mm}^3$ )	0.2	0.1
- thrombocytopenia ( $0 \leq x < 100,000/\text{mm}^3$ )	0.1	0.2
Skin disorders:		
- rash	4.2*	3.5
- severe†	0.1	0.1
- leading to discontinuation†	0.5	0.2
- pruritus	3.3*	1.6
Gastrointestinal disorders:		
- peptic, gastric, duodenal ulcer	0.7	1.2
- diarrhea	4.5*	3.4
- severe†	0.2	0.1
- leading to discontinuation†	0.4	0.3
- dyspepsia	5.2	6.1*
- constipation	2.4	3.3*
- stomatitis	0.2	0.1
- nausea	3.4	3.8
- abdominal pain	5.6	7.1*
- gastritis	0.8	1.3*
Cardiovascular and rhythm disorders:		
- heart and rhythm disorder	4.3	5.0*
- pulmonary embolism	0.4	0.2
Other:		
- allergic reaction	0.9	1.0
- influenza-like symptoms	7.5	7.0
- fatigue	3.3	3.4
- pain	6.4	6.3
- headache	7.6	7.2
- coughing	3.1	2.7

\* Statistically significant difference between treatments ( $p \leq 0.05$ )

† Patients may be included in more than one category

**CURE:** The clinically important adverse events observed in CURE are discussed below:

In CURE, PLAVIX was given with ASA, and was not associated with a significant increase in life-threatening or fatal bleeds compared to placebo given with ASA; the incidences of non-life threatening major bleeding and minor bleeding were significantly larger in the PLAVIX + ASA group. The incidence of intracranial hemorrhage was 0.1% in both groups. There was an excess in major bleeds, primarily gastrointestinal and at puncture sites. In patients receiving both PLAVIX and ASA in CURE, the incidence of bleeding is described in Table 6 below:

Table 6: CURE Incidence of Bleeding Complications (% Patients)

Event	PLAVIX+ASA* (N=6256)	Placebo+ASA* (N=6303)	p-value
Life-threatening bleeding	2.2	1.8	0.13
Fatal	0.2	0.2	
5 g/dL hemoglobin drop	0.9	0.9	
Requiring surgical intervention	0.7	0.7	
Hemorrhagic strokes	0.1	0.1	
Requiring intropres	0.5	0.5	
Requiring transfusion ( $\geq 4$ units)	1.2	1.0	
Other major bleeding	1.6	1.0	0.005
Significantly disabling	0.4	0.3	
Intraocular bleeding with significant loss of vision	0.05	0.03	
Requiring 2-3 units of blood	1.3	0.9	
Major bleeding†	3.7†	2.7‡	0.001
Minor bleeding†	5.1	2.4	< 0.001
Total with bleeding complications	8.5	5.0	< 0.001

\* Other standard therapies were used as appropriate. All patients received ASA 75-325 mg daily (mean=160 mg)

† Life threatening and other major bleeding necessitating transfusion of  $\geq 2$  units of blood.

‡ Major bleeding event rate for PLAVIX + ASA was dose-dependent on ASA: <100 mg=2.6%; 100-200 mg=3.5%; >200 mg=4.9%

§ Major bleeding event rate for placebo + ASA was dose-dependent on ASA: <100 mg=2.0%; 100-200 mg=2.3%; >200 mg=4.0%

¶ Led to interruption of study medication.

The number of patients with bleeding that met the criteria for major bleeding established by the Thrombolysis in Myocardial Infarction (TIMI) trial was 68 (1.09%) in the clopidogrel group and 73 (1.16%) in the placebo group (relative risk, 0.94;  $p=0.70$ ). The number with bleeding that met the criteria for life-threatening or severe bleeding established by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial was 78 in the clopidogrel group and 70 in the placebo group (relative risk, 1.12;  $p=0.48$ ). Some patients had more than one bleeding episode.

Ninety-two percent (92%) of the patients in the CURE study received unfractionated or low molecular weight heparin, and the rate of bleeding in these patients was similar to the overall results.

There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.6% PLAVIX + ASA; 5.5% placebo + ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 8.9% for PLAVIX + ASA, and 6.2% for placebo + ASA, which was not significantly different.

**Thrombocytopenia:** In CURE, the number of patients with thrombocytopenia (19 PLAVIX + ASA versus 24 placebo + ASA) or neutropenia (3 versus 3) was similar.

**Gastrointestinal:** In the CURE trial, the incidence of gastrointestinal events (e.g., abdominal pain, dyspepsia, gastritis and constipation) for patients receiving PLAVIX + ASA was 11.7% compared to 12.5% for those receiving placebo + ASA. The incidence of peptic, gastric or duodenal ulcers was 0.4% for PLAVIX + ASA and 0.3% for placebo + ASA. The incidence of diarrhea for patients receiving PLAVIX + ASA was 2.1% compared to 2.2% for those receiving placebo + ASA. The incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 0.9% for PLAVIX + ASA compared with 0.8% for placebo + ASA.

**Rash and other skin disorders:** In the CURE trial, the incidence of rash or other skin disorders in patients receiving PLAVIX + ASA was 4.0% compared to 3.5% for those receiving placebo + ASA. In the CURE trial, the incidence of patients withdrawing because of skin and appendage disorder adverse reactions was 0.7% for PLAVIX + ASA compared with 0.3% for placebo + ASA.

**Post Marketing Experience:** The following additional adverse reactions were reported in marketed use, however a causal relationship with clopidogrel has not been clearly established.

**Skin disorders:** Maculopapular or erythematous rash, urticaria, pruritus. Very rarely: angioedema, bullous eruption (erythema multiforme).

**Musculo-skeletal disorders:** Very rarely: arthralgia, arthritis.

**Collagen disorders:** Very rarely: vasculitis.

**Neurological disorders:** Very rarely: confusion, hallucinations, taste disorders.

**Gastro-intestinal disorders:** Very rarely: colitis (including ulcerative or lymphocytic colitis).

**Liver and biliary disorders:** Very rarely: abnormal liver function test, hepatitis.

**Respiratory system disorders:** Very rarely: bronchospasm.

**Hematological disorders:** Very rarely: serious cases of bleeding, mainly skin, musculo-skeletal, eye (conjunctival, ocular, retinal) and respiratory tract bleeding, epistaxis, hematuria and hemorrhage of operative wound, hematoma; cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage). Very rarely: agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP). TTP was not observed in clinical studies involving more than 11,300 patients receiving clopidogrel (including over 7,000 patients treated for one year or more).

**Urinary system disorders:** Very rarely: glomerulopathy, abnormal creatinine levels.

**Allergic disorders:** Very rarely: anaphylactoid reactions, fever.

## DOSE AND ADMINISTRATION

**MI, Stroke or Established Peripheral Arterial Disease:** The recommended dose of PLAVIX is 75 mg once daily long term with or without food.

**Acute Coronary Syndrome:** PLAVIX should be initiated with a 300 mg loading dose and continued long term at 75 mg once a day with ASA (80 mg-325 mg daily).

No dosage adjustment is necessary for elderly patients or patients with renal impairment.

## AVAILABILITY OF DOSAGE FORMS

PLAVIX (clopidogrel bisulfate) is available as pink, round, slightly biconvex, film-coated tablets engraved with "75" on one side and "1171" on the other side, available in cartons containing a blister of 28 tablets and bottles containing 500 tablets.

Product Monograph available upon request.

**REFERENCES:** 1. Harker LA, et al. Comparative safety and tolerability of clopidogrel and aspirin. *Drug Safety* 1999;21(4):325-35. 2. Hankey GJ. Current oral antiplatelet agents to prevent atherothrombosis. *Cerebrovasc Dis* 2001;11(Suppl 2):11-17. 3. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996;348:1329-39. 4. CURE Study Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345(7):494-502. 5. PLAVIX Product Monograph. Sanofi-Synthelabo Canada Inc., April 27, 2004.

PLAVIX® is a registered trademark of Sanofi-Synthelabo Canada Inc., used under licence. Laval, Quebec H7L 4A8.

An agreement between Bristol-Myers Squibb and sanofi-aventis for the codevelopment and marketing of irbesartan and clopidogrel, two compounds from sanofi-aventis research.

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## in brief

### Chemo drug eases colon CA treatment

British researchers are espousing the benefits of the oral chemotherapeutic drug capecitabine (Xeloda) in the adjuvant treatment of advanced colon cancer patients. Compared with the current standard of care, fluorouracil plus leucovorin (5-FU/LV), capecitabine was found to offer similar efficacy but with improved convenience to the patient. Intravenous 5-LU/FV treatment for colon cancer can require up to 30 clinic visits over a 24-week treatment course compared with just eight visits over the same time for patients receiving capecitabine. Findings from the randomized control study, which involved 1,987 stage III colon cancer patients, appeared in the *New England Journal of Medicine*. The researchers found the three-year disease-free survival rates were 64.2% for patients treated with capecitabine versus 60.6% for those treated with 5-LU/FV.

### Drug may undo harm of platinum in CA therapy

Researchers at the Moores University of California at the San Diego Cancer Centre are leading a national phase III trial to determine if the drug amifostine (Ethyol), which is used to protect the gums, cheeks and mucosa in the throat during radiotherapy for head and neck cancers, can reverse the debilitating symptoms of peripheral neuropathy that some cancer patients taking platinum-based drugs experience. While the researchers don't fully understand how the drug may work to reverse peripheral neuropathy, they say there are clues that platinum binds to a part of the neural tissue and amifostine acts to uncouple that bond. For the prospective trial involving 25 centres, half of participants will receive amifostine for 12 weeks and the other half will be observed.

### Give men drugs to treat sexual partners: study

Researchers at Tulane University School of Public Health and Tropical Medicine in New Orleans report in *Clinical Infectious Diseases* that sexually transmitted disease treatment can be effectively administered by sex partners. They found that men with chlamydia or gonorrhoea were more likely to talk to their female partners about the STD when given medicine to give their partners than were men who were simply told to inform their partners. The researchers enrolled 977 men from an STD clinic in New Orleans. About 70% of the men in the patient-delivered partner treatment arm of the study intervened with their partners, compared with 48% of men in the standard partner referral arm.