Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs

| Study, Year  (N) | Study Design | Country | Study Funding | Quality Rating | Innovator Product (Manufacturer), Dose | Generic Product (Alternate Name, Manufacturer), Dose | Followup | Inclusion Criteria | Exclusion Criteria |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Unspecified Innovator and Brand Antiepileptic Drug Products | | | | | | | | | |
| Zachry,2009  (N=1664) | Retrospective Observational  (Case-control) | United States | Abbott Laboratories sponsored the study and three authors were employees | Fair – Retrospective, uses case-control methodology which has more inherent limitations, did not control for factors other than epilepsy diagnosis code and age. Uses claims data which cannot identify actual product use. Claims data may have coding errors. Drugs and doses not reported | Innovator antiepileptic | “A” rated generic antiepileptic | Six months before the index date | Cases :  Received ambulance transport, emergency department visitation, or inpatient hospitalization for epilepsy occurred between July 1 and December 31, 2006 (the index date).  Controls: Ambulatory office visit for with a primary diagnosis of epilepsy between July 1 and December 31, 2006 (the index date) | ICD-9 code for infantile spasms, aged below 12 or over 64 years of age, or did not have continuous insurance coverage for 6 months before the index date  Cases were matched 3:1 for age and ICD-9 codes to controls, other controls were excluded |

| Table F-1. Study design and populations of controlled studies comparing innovator versus generic antiepileptic drugs (continued) | | | | | | | | | |
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| Study, Year  (N) | Study Design | Country | Study Funding | Quality Rating | Innovator Product (Manufacturer), Dose | Generic Product (Alternate Name, Manufacturer), Dose | Followup | Inclusion Criteria | Exclusion Criteria |
| Rascati, 2009  (N=3964) | Retrospective  Observational  (Case-control) | United States | Unrestricted educational grant from Abbott Laboratories | Fair – Retrospective, uses case-control methodology which has more inherent limitations, did not control for factors other than epilepsy diagnosis code and age. Uses claims data which cannot identify actual product use. Claims data may have coding errors. Drugs and doses not reported | Various | Various  Only “A” rated generics were evaluated | - | Patients with and ICD-9 code for epilepsy (excluding infantile spasm) in the PharMetrics database (a database accounting for 55 million patients from across the United States) between 12 and 64 years of age, continuous insurance coverage and a prescription for antiepileptic drugs for 145 days.  Cases were identified if they had an epilepsy related acute event (ambulance service, emergency department visit, or hospitalization) between Oct. 1, 2005 and Dec. 31, 2006 and no acute event 6 months prior.  Controls were identified if they had epilepsy and visited a doctor’s office during the same time period but did not have an acute event. | Patients with an ICD-9 code for infantile spasms  Cases were matched 3:1 for age (within 5 years), gender, and ICD-9 codes to controls, other controls were excluded |
| Devine, 2010  (N=11796)  ESI Study | Retrospective Observational Cohort study | United States | Express Scripts, Inc. | Fair – Retrospective, uses case-control methodology which has more inherent limitations, controlled for factors such as epilepsy diagnosis code, age, gender, geographical location, co-morbidities, disease severity, interacting medication, non-adherence, patient diagnosis, baseline disease state, and time. Uses claims data which cannot identify actual product use. Claims data may have coding errors. Drugs and doses not reported | Various | Various  Only “A” rated generics were evaluated | 90 days before the index date | The study population was made up of individuals with stable epilepsy and AED use during the last 6 months of 2005. Patients were included in the study if they: (1) had a primary or secondary diagnosis of epilepsy, (2) had a prescription claim for an AED with a days’ supply carrying over through January 1, 2006, (3) had eligibility for medical and prescription benefit coverage as of July 1, 2005 through June 30, 2006, and (4) were between the ages of 18 and 64 (inclusive) as of January 1, 2006 | Patients younger than 18 years old were not included in the study due to unstable hormone levels increasing their risk for epilepsy exacerbations. Patients 65 years and older were not included because they are not represented in the MarketScan commercial database.  Patients were excluded when there was one or more inpatient or emergency room claim with a primary diagnosis of epilepsy between July 1 and December 31, 2005, as patients with a recent history of exacerbation of epilepsy may be at high risk for repeat seizures |
| Labiner, 2010a  (N=18125) | Retrospective  Observational  Cohort study | United States | GlaxoSmithKline  One author is an employee of GlaxoSmithKline | Poor – Not limited to “A” rated generics, dosing may or may not have been similar, administrative claims data does not have several potentially relevant confounders (including disease severity), there may be inaccuracies in coding of diagnoses and procedures, whether drugs dispensed were consumed and how were consumed is not known, if limited to innovator or branded generics is not known, exact brand names and forms included not reported | Branded carbamazepine, phenytoin, primidone, zonisamide (if limited to innovator or branded generics is not known, exact brand names and forms included not reported) | Carbamazepine gabapentin, phenytoin, primidone, zonisamide  (Manufacturers not reported) | From target medication dispensing until 30 days after the last drug supply was obtained, health coverage ended, or the end of data availability, whichever occurred first. Mean observation period ~ 4 years | Patients 18 years or older with 2 or more years of continuous health plan e-ollment, an ICD-9 code for nonfebrile convulsions (ICD-9: 780.3 or 780.39), dispensing of target drugs (carbamazepine, gabapentin, phenytoin, primidone, zonisamide) at least twice, and at least 60 days worth of drugs dispensed during the first 90 days of treatment. Stable patients only | For gabapentin, only monotherapy use was permitted to reduce the risk of use in nonepilepsy indications |
| Labiner, 2010b  (N=15500) | Retrospective  Observational  Cohort study | United States | GlaxoSmithKline  One author is an employee of GlaxoSmithKline | Poor – Not limited to “A” rated generics, dosing may or may not have been similar, administrative claims data does not have several potentially relevant confounders (including disease severity), there may be inaccuracies in coding of diagnoses and procedures, whether drugs dispensed were consumed and how were consumed is not known, if limited to innovator or branded generics is not known, exact brand names and forms included not reported | Branded carbamazepine, phenytoin, primidone, zonisamide (if limited to innovator or branded generics is not known, exact brand names and forms included not reported) | Carbamazepine gabapentin, phenytoin, primidone, zonisamide | From target medication dispensing until 30 days after the last drug supply was obtained, health coverage ended, or the end of data availability, whichever occurred first. Mean observation period ~ 4 years | Patients 18 years or older with 2 or more years of continuous health plan e-ollment, an ICD-9 code for nonfebrile convulsions (ICD-9: 780.3 or 780.39), dispensing of target drugs (carbamazepine, gabapentin, phenytoin, primidone, zonisamide) at least twice, and at least 60 days worth of drugs dispensed during the first 90 days of treatment. Unstable patients only | For gabapentin, only monotherapy use was permitted to reduce the risk of use in nonepilepsy indications |
| Carbamazepine | | | | | | | | | |
| Kauko, 1974  (N=20) | Two Concurrently run unblinded “before and after” trials | Finland | Drug provided by Ciba-Geigy | Poor – Before and after evaluations, exclusion criteria and demographics not well described, only pharmacokinetic endpoints evaluated, no measure of AUC, not an “A” rated generic in the United States | Tegretol (Ciba-Geigy) tablets 15.6 mg/kg/day | Carbamazepine (Laake Oy) 15.6 mg/kg/day  Not an “A” rated generic in the United States | 20 weeks | In the first trial, patients had to be taking generic carbamazepine at baseline.  In the second trial, patients had to be taking Tegretol at baseline | - |
| Glende, 1983  (N=5) | Ramdomized crossover design | Germany | Unknown |  | Tegretol (Ciba-Geigy) tablets | Carbamazepine (AWD Dresden)  Not an “A” rated generic in the United States | 4 weeks (2 weeks per phase) | The patients had been receiving carbamazepine for several years | - |
| Jumao-as, 1989  (N=10) | Randomized  Double-blind  Crossover | United States | Veterans Administration and University of Pittsburgh | Fair – Demographics not well described, dose of carbamazepine not reported, not an “A” rated generic in the United States | Tegretol (Ciba-Geigy) tablets | Carbamazepine (Parke-Davis) tablets  Not currently an “A” rated generic in the United States | 10 weeks (5 weeks per phase) | The patients had to be receiving carbamazepine prior to entry and had at least 1 seizure in the past year. | - |
| Hartley, 1990  (N=23) | Randomized  Crossover  Blinding not reported | United Kingdon | Ciba-Geigy funded the study and provided carbamazepine tablets. UK Generics provided the generic tablets | Fair – Short duration of followup, not an “A” rated generic in the United States | Tegretol (Ciba-Geigy) Tablets 16.2 mg/kg/day | Carbamazepine (United Kingdom Generics) 16.2 mg/kg/day  Not an “A” rated generic in the United States | 12 weeks (6 weeks per phase) | Patients needed to experience at least 3 seizures in the past to be included | - |
| Hartley, 1991  (N=12) | Randomized  Crossover  Blinding not reported | United Kingdom | - | Fair – Blinding not reported, exact dose of carbamazepine not reported, not an “A” rated generic in the United States | Tegretol (Ciba-Geigy) Tablets ~20mg/kg/day | Carbamazepine (Ethical Generics) Tablets ~20mg/kg/day  Not an “A” rated generic in the United States | 12 weeks (6 weeks per phase) | - | - |
| Oles, 1992a  (N=20) | Randomized  Double-blind  Crossover | United States | Financial support: Lemmon Co;  Drug: Ciba-Geigy | Good – | Tegretol (Ciba-Geigy) Tablets 12.4 (3.5) mg/kg daily | Carbamazepine (Lemmon Co) Tablets 12.4 (3.5) mg/kg daily  An “A” rated generic in the United States | 6 months (3 months in each phase with pharmacokinetics determined 2 weeks into each phase) | Patients had to be seizure-free for over 5 months | Taking carbamazepine for less than 6 months, and hepatic or renal disease |
| Oles, 1992b  (N=20) | Randomized  Double-blind  Crossover | United States | Financial support: Lemmon Co;  Drug: Ciba-Geigy | Good - Followup was brief | Tegretol (Ciba-Geigy) Tablets 21.9 (6.2) mg/kg daily | Carbamazepine (Lemmon Co) Tablets 21.9 (6.2) mg/kg daily  An “A” rated generic in the United States | 6 months (3 months in each phase with pharmaco- kinetics determined 2 weeks into each phase) | Patients had to have refractory seizures. | Taking carbamazepine for less than 6 months, and hepatic or renal disease |
| Reunanen, 1992  (N=21) | Randomized  Single-blind  Crossover | Finland | - | Poor – Single-blinded, not an “A” rated generic in the United States, short duration of followup | Tegretol Retard (Ciba-Geigy) Tablets 685 (268) mg/day | Carbamazepine (Laakefarmos) Tablets 685 (268) mg/day  Not an “A” rated generic in the United States | 4 weeks (2 weeks per phase) | Patients age 18-65 years with epilepsy | Seizure within the past 4 months; severe psychiatric, renal, hepatic, gastrointestinal, other disease that impact absorption; drug or alcohol abuse |
| Silpakit, 1997  (N=18) | Randomized  Double-blind  Three phase Crossover | Thailand | Srithanya Hospital Fund | Fair – Not an “A” rated generic in the United States, short duration of followup | Tegretol (Ciba-Geigy) Tablets 677.8 (155.5) mg/day | Carbamazepine (Central Poly) 677.8 (155.5) mg/day  Carbamazepine (Condrugs) 677.8 (155.5) mg/day  Carbamazepine (Pharmaland) 677.8 (155.5) mg/day  Not an “A” rated generic in the United States | 12 weeks (3 weeks each phase) | Patients had to have epilepsy, epilepsy with psychosis, or temporal lobe psychosis | Seizure free for <5 months, abnormal renal or liver function, electrolyte of blood count abnormalities |
| Aldenkamp, 1998  (N=12) | Randomized  Open-Label  Crossover | Netherlands | Unknown | Fair – Not an “A” Rated Generic in the United States, Open Label | Tegretol (Ciba-Geigy) Tablets  Average dose for all products:  717 (180)mg | Carbamazepine (Pharmachemie) Tablets  Carbamazepine (Pharbita) Tablets  Average dose for all products 717 (180)mg  Not an “A” rated generic in the United States | 9 days total, 3 days per therapy | Outpatients with average intelligence with ages between 18 and 60 years. Epilepsy treated with carbamazepine monotherapy for >2 months | Psychiatric, heart, liver, kidney, thyroid, pulmonary, or hematologic disorders; neurological deficits other than epilepsy; or use of non-antiepileptic neurological agents except modest alcohol intake |
| Garnett, 2005  (N=980) | Retrospective  Observational  (Cohort) | United States | Shire US, Inc | Poor – Retrospective design, data on outcomes not adjusted for confounders, dose not controlled, some changes in CBZ exposure after study entry, not limited to “A” rated generics | Tegretol (Novartis) Tablets | Carbamazepine Tablets  Not limited to “A” rated products | - | Patients 18 years or older with ICD-9-CM codes for epilepsy and started on immediate release carbamazepine between 1999 and 2001 in the PharMetrics database | Incomplete data records or a history of pre-existing conditions (aplastic anemia, agranulocytosis, Lyell’s or Stevens-Johnson syndrome, psychosis, brain cancer, visual disturbances, ataxia, confusion, diplopia, or vertigo |
| LeLorier, 2008d  (N=851) | Retrospective  Observational  (Cohort study) | Canada | GlaxoSmithKline sponsored and participated in the design, review, and approval of the manuscript |  | Tegretol CR | Carbamazepine  Whether they were “A” rated products in the United States is not known. Whether only sustained release generics were allowed in the study is not known | Mean duration of observation 1,117 (307.6) days | Patients with medical and pharmacy claims in Quebec’s provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Tegretol CR for at least sixty days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy | - |
| Clobazam | | | | | | | | | |
| Andermann, 2007b  (N=1600) | Retrospective  Observational Before-and-after | Canada | GlaxoSmithKline | Poor – Database could not be limited those with epilepsy. Does not account for confounders. Time related biases exist, whether only “A” rated generics were used is not known | Frisium | Clobazam (manufacturers not reported)  Whether only “A’ rated generics were used is not known | The study period ranged from 1 year before generic entry to March 2006 | Patients who continuously used Frisium for 3 or more months in the 6 months preceding generic entry. | Patients who were not switched to the generic counterpart |
| LeLorier, 2008b  (N=1060) | Retrospective  Observational  (Cohort study) | Canada | GlaxoSmithKline sponsored and participated in the design, review, and approval of the manuscript | Poor – Retrospective, whether generics were “A” rated was unknown, no attempts made to correct for baseline differences | Frisium | Clobazam  Whether they were “A” rated products in the United States is not known | Mean duration of observation 1,090 (329.4) days | Patients with medical and pharmacy claims in Quebec’s provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Frisium for at least 60 days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy | - |
| Gabapentin | | | | | | | | | |
| LeLorier, 2008c  (N=202) | Retrospective  Observational  (Cohort study) | Canada | GlaxoSmithKline sponsored and participated in the design, review, and approval of the manuscript | Poor – Retrospective, whether generics were “A” rated was unknown, no attempts made to correct for baseline differences | Neurontin | Gabapentin  Whether they were “A” rated products in the United States is not known | Mean duration of observation 1,019 (351.5) days | Patients with medical and pharmacy claims in Quebec’s provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Neurontin for at least 60 days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy | - |
| Lamotrigine | | | | | | | | | |
| Andermann, 2007a  (N=1142) | Retrospective  Observational  Before-and-after | Canada | GlaxoSmithKline | Poor – Database could not be limited those with epilepsy. Does not account for confounders. Time related biases exist, whether only “A” rated generics were used is not known | Lamictal  Group who switched to generic and then switched back: 252.2 mg and 250.7 mg.  Group who switched to generic but did not switch back: 255.3 mg | Lamotrigine (manufacturers not reported)  Group who switched to generic and then switched back: 254.6 mg.  Group who switched to generic but did not switch back: 271.1 mg  Whether only “A’ rated generics were used is not known | The study period ranged from 1 year before generic entry to March 2006 | Patients who continuously used Lamictal for 3 or more months in the 6 months preceding generic entry. | Patients who were not switched to the generic counterpart |
| LeLorier, 2008a  (N=671) | Retrospective  Observational  (Cohort study) | Canada | GlaxoSmithKline sponsored and participated in the design, review, and approval of the manuscript | Poor – Retrospective, whether generics were “A” rated was unknown, no attempts made to correct for baseline differences | Lamictal (GlaxoSmithKline) 239.1 mg/day | Lamotrigine (manufacturer(s) not reported) 251.4 mg/day  Whether they were “A” rated products in the United States is not known | Mean duration of observation 1,098 (327.9) days | Patients with medical and pharmacy claims in Quebec’s provincial health plan from April 1998 to July 2006. Patients were eligible 180 days before generic entry into the market, used Lamictal for at least sixty days in the 90 days preceding the generic entry date, had one drug dispensation following the generic entry date, had continuous health plan coverage, and having an ICD-9 code for epilepsy | - |
| Nielsen, 2008a  (N=9) | Before-and-after  Unblinded | Denmark | Funding for the study was not reported but one author was on the UCB advisory board and another author has received speaker fees and sponsorship from several pharmaceutical companies | Poor – Before and after design, multiple generics being compared to a single innovator product, small sample size, population all had concerns or problems on generic medication in the past, not “A” rated generics in the United States, short duration of followup | Lamictal 755.6 (202) mg | Lamotrigine (Copyform, Hexal, Ratiofarm, Ratiopharm, Farma, Actavis, Stada) 755.6 (202) mg  Generics stated to be bioequivalent with innovator lamotrigine.  Not “A” rated generics in the United States | 17 days, patients were on Lamictal for 2 weeks and then on a generic for 7-15 days | Patients had to have reported a problem after switching from innovator to generic to be eligible for entry into the trial | - |
| Levetiracetam, Oxcarbazepine, Phenobarbital or Primidone, Phenytoin | | | | | | | | | |
| Lund, 1974  (N=9) | Prospective  Before-and-after | Sweden | Swedish Medical Research Council | Poor  Sequential, not randomized | Epanutin (Parke-Davis) capsules, 100 mg  Patients continued on same dose from baseline | Phenytoin sodium (Leo) capsules, 100 mg  Patients continued on same dose from baseline | Epanutin days 1 to 8, phenytoin sodium days 9-19 | Epileptic outpatients | - |
| Chen, 1982  (N=18) | Prospective  Crossover | United Kingdom | - | Poor  Sequential, not randomized.  Different dosage forms compared (tab vs cap) | Epanutin (Parke-Davis) capsules, 100 mg, 50 mg  Patients continued on same dose from baseline\ | Phenytoin sodium (Boots) tablets, 100 mg, 50 mg  Phenytoin sodium (Cox) tablets, 100 mg, 50 mg  Phenytoin sodium (Kerfoot) tablets, 100 mg, 50 mg  Phenytoin sodium (McCarthy UK) tablets, 100 mg, 50 mg  Patients continued on same dose from baseline | 3 weeks per product | Aged 26 to 68 years on long-term treatment with phenytoin | - |
| Hodges, 1986  (N=30) | Randomized  Crossover | United Kingdom | Parke-Davis | Fair  Not the same dosage form compared | Phenytoin (Parke-Davis) capsules, 50 mg  Dose ranged from 5 to 7.5 mg/kg/day | Phenytoin (Boots) tablets, 50 mg  Phenytoin (Evans) tablets, 50 mg Dose ranged from 5 to 7.5 mg/kd/day | 4 weeks per product | New patients between 3 and 15 years | - |
| Kishore, 1986  (N=60) | Randomized  Parallel | India | - | Fair  Blinding uncertain | Dilantin (Parke-Davis, India) capsules, 100 mg  In patients weighing <55kg, 200 mg/day  In patients ≥55 kg, 300 mg/day | Phenytoin (Epsolin, Cadila) tablets, 100 mg  Phenytoin (Eptoin, Boots India) tablets, 100 mg  Phenytoin (Epileptin, Indian Drugs and Pharmaceuticals) capsules, 100 mg  Salt forms not reported  In patients weighing <55kg, 200 mg/day  In patients ≥55 kg, 300 mg/day | 3 months | Newly diagnosed epilepsy patients | - |
| Mikati, 1992  (N=10) | Randomized  Crossover  Double-blinded | United States | - | Fair  Not all patients with epilepsy.  Sample size small | Dilantin (Parke-Davis) capsule, 100 mg | Phenytoin (Phenytex, manufacturer not reported) capsules, 100 mg | 3 months per product | Adults aged 18 to 60 years receiving phenytoin monotherapy for seizure prophylaxis.  All but one had partial or generalized seizures. One patient was receiving phenytoin prophylaxis after intracranial surgery | Patients judged to have poor compliance or judged to be u-eliable in reporting the necessary information, side effects, or seizures |
| Soryal, 1992  (N=14) | Randomized  Crossover  Observer-blinded | United Kingdom | - | Fair  Different dosage forms | Epanutin (Parke-Davis) capsules, 100 mg, 50 mg  Patients continued on same dose from baseline | Phenytoin sodium (Evans) tablets, 100 mg, 50 mg  Phenytoin sodium (APS) tablets, 100 mg, 50 mg  Phenytoin sodium (Cox) tablets, 100 mg, 50 mg  Phenytoin sodium (Kerfoot) tablets, 100 mg, 50 mg  Phenytoin sodium (Regent) tablets, 100 mg, 50 mg  Patients continued on same dose from baseline | 4 weeks per product | Patients with epilepsy from the Epilepsy Unit on maintenance treatment with phenytoin | - |
| Topiramate | | | | | | | | | |
| Duh, 2009  (N=948) | Retrospective  Observational  Registry database | Canada | Ortho-McNeil Janssen Scientific Affairs | Poor | Topamax (Ortho-McNeil) | Topiramate (Various manufacturers)  Also provided switchback rates for:  Lamotrigine  Gabapentin  Divalproex  Clobazam  Clonazepam  Valproate  Carbamazepine | Starting 180 days before generic entry or January 2000, through the end of patient eligibility, treatment discontinua- tion or October 2007 | Patients from the RAMQ database with epilepsy with continuous health plan coverage, treated for at least 60 days with the branded version of one of the AED or non-AED study drugs before the generic entry date, and at least one dispensing of the studied drug (brand or generic) following generic entry, and continuous use of the studied drug throughout the study period | - |
| Paradis, 2009a  (N=1164) | Retrospective  Observational  Registry database | Canada | Janssen-Cilag EMEA | Poor | Topamax (Ortho-McNeil) | Topiramate (Various manufacturers) | From January 2006 to September 2008 | Patients from the RAMQ database with epilepsy with continuous health plan coverage, treated for at least 60 days with the branded version of one of the AED or non-AED study drugs before the generic entry date, and at least one dispensing of the studied drug (brand or generic) following generic entry, and continuous use of the studied drug throughout the study period | - |
| Valproic Acid | | | | | | | | | |
| Vadney, 1997 (N=64) | Randomized  Crossover  Open-label | United States | Texas Department of Mental Health and Mental Retardation | Fair  Not blinded | Depakene (Abbott) | Valproic acid (Solvay) | 4 weeks per product | Patients at an Intermediate Care Facility for the Mentally Retarded who were already receiving either valproic acid or Depakene for primary diagnosis of seizure disorder | Individuals who could not be at the facility for consistent observation, those who required any change in an antieptileptic drug or psychotropic medication, or residents who experienced toxicity |
| Andermann, 2007c  (N=2017) | Retrospective  Observational  Before-and-after | Canada | GlaxoSmithKline | Poor – Database could not be limited those with epilepsy. Does not account for confounders. Time related biases exist, whether only “A” rated generics were used is not known | Depakene | Valproic Acid (manufacturers not reported)  Whether only “A” rated generics were used is not known | The study period ranged from 1 year before generic entry to March 2006 | Patients who continuously used Depakene for 3 or more months in the 6 months preceding generic entry | Patients who were not switched to the generic counterpart |

- = not reported; N = sample size aReports on same database as Duh 2009