

Appendix 12 (as supplied by the authors): Adverse events (excluding hypoglycemia) reported in randomized controlled trials of rapid-acting insulin analogues in type 1 diabetes

Study*	Treatment arms	Description of adverse events
Ampudia-Blasco, ²¹ 2005	IAsp ILis HI	NR
Anderson, ²⁴ 1997	ILis+NPH or UL HI+NPH or UL	Most common AEs: headache, pharyngitis, infection, rhinitis, flu syndrome, pain, accidental injury, and diarrhea reported by 5-15% of patients. No difference between the two treatments
Anderson, ³⁶ 1997	ILis+basal HI+basal	There was no difference in the frequency or type of AE between the two treatment groups. The most common AE were flu syndrome, pharyngitis, rhinitis, other infections, or headache. No local reactions in the injection site were reported in the pts treated with insulin lispro.
Annuzzi <i>et al.</i> , 2001 ²⁵	ILis+NPH HI+NPH	A slight and similar increase in body weight was associated with both treatments. No difference was observed in the blood lipid concentration.
Arslanian, ²⁶ 2005	IAsp+NPH ILis+NPH	Number and types of TEAEs not reported but it is stated that there were no notable differences in the occurrence of AEs between treatments. IAsp: 5% of patients reported diabetic ketoacidosis. 2 patients (4.9%) withdrew due to AEs. ILis: 3% of patients reported diabetic ketoacidosis. None withdrew due to AEs. HI: 2% of patients reported diabetic ketoacidosis. 3 patients (13.6%) withdrew due to AEs
Bode, ²⁷ 2002	IAsp+basal ILis+basal HI+basal	AEs reported as similar profiles for all groups and reported by ~70% patients. One patient in IAsp group withdrew because of herpes zoster; most AEs were mild.
Bode, ²⁸ 2001	IAsp+basal HI+basal	AEs, most commonly upper respiratory infections, were reported by 6 (32%) patients in the IAsp group and 3 (30%) in the HI group. No injection site reactions were reported by patients in either group.
Bott <i>et al.</i> , 2003 ²⁹	IAsp HI	NR
Caixàs <i>et al.</i> , 1998 ³⁰	ILis+UL HI+UL	NR
Chan <i>et al.</i> , 2004 ³³	ILis+NPH HI+NPH	Mild weight gain of 1.1 kg were observed at the end of the study, but there was no difference between the two arms (P=0.342)
Ciofetta <i>et al.</i> , 1999 ³¹	ILis+NPH ILis/NPH+NPH HI+NPH	NR
Deeb, ⁶³ 2001	ILis (before meal) +basal ILis (after meal)+basal HI (before meal)+basal	No significant differences in AEs were observed among the 3 therapies. The most common AEs were: rhinitis, pharyngitis, cough and fever, none of which showed a relationship to insulin therapies.
Del Sindaco <i>et al.</i> , 1998 ⁶⁴	ILis NPH	It was reported that body weight did not change in any of the group (Data not shown in the original paper)
Fairchild, ¹⁹ 2000	ILis+NPH NPH+ILis	No other adverse events could be attributed to insulin lispro, however, one boy, with a past history of lipoatrophy on other insulins, developed lipoatrophy at the end of three months on lispro

Ferguson <i>et al.</i> , 2001 ⁶⁵	HI+NPH ILis+NPH	NR
Ford-Adams <i>et al.</i> , 2003 ⁶⁶	ILis+NPH HI+NPH	NR
Gale, 2000 ⁶⁷	ILis+basal HI+basal	NR
Garg <i>et al.</i> , 1996 ⁶⁸	ILis+NPH or UL	The number of severe insulin reactions was similar for the two groups with the exception of one patient in early renal failure in the insulin lispro group who had 9 severe reactions in the 12 month period. He also had frequent severe reactions prior to entering the study. Among the remainder of the subjects, there were a total of 8 severe reactions in the insulin lispro treated patients and 12 in the control group over the 12 months period(P>0.05, Fisher Exact Test)
Hedman <i>et al.</i> , 2001 ⁶⁹	HI+NPH or UL ILis+basal	NR
Heller <i>et al.</i> , 1999 ⁷⁰	ILis+NPH HI+NPH	NR
Heller <i>et al.</i> , 2004 ⁷¹	IAsp+NPH HI+NPH	NR
Holcombe, ⁷² 2002	ILis+NPH IAsp+NPH	Most common AEs were rhinitis, pharyngitis, and flu syndrome. None were judged to be related to treatment. No differences observed between the 2 treatments.
Holleman <i>et al.</i> , 1997 ⁷³	ILis+NPH HI+NPH	NR
Home, ⁷⁶ 2006	IAsp+NPH HI+NPH	IAsp: 469 patients (83%) experienced 2980 AEs; 62 patients (11%) experienced 87 serious AEs; 459 patients (81%) experienced 2893 non-serious AEs HI: 140 patients (75%) experienced 802 AEs; 22 patients (12%) experienced 29 serious AEs; 136 patients (73%) experienced 774 non-serious AEs
Home, ⁷⁵ 2000	IAsp+NPH HI+NPH	All AEs leading to withdrawal from IAsp were due to hypoglycemia except one case of urticaria and one death from myocardial infarction (both assessed as unrelated to treatment). Each arm had 3 events of ketoacidosis. IAsp: 1600 events/484 patients (4.6 events/pt yr) HI: 752 events/233 patients (4.4 events/pt yr)
Home, ⁷⁴ 1998	IAsp+NPH HI+NPH	One patient with fatigue and anorexia in IAsp arm resulted in withdrawal. Serious AEs during IAsp involved vomiting and pyrexia in 1 patient, hypoglycemia with convulsions in 1 patient. Serious AEs during HI arm involved confusion in 1 patient and hypoglycemia with convulsions in 1 patient.
Iwamoto, ⁷⁷ 2001	IAsp+basal HI+basal	AEs included dizziness, retinal disorder, nausea, abdominal pain, metabolic disorders, dyspnea, amenorrhea, malaise, and injection site reaction. IAsp: 11 events probably related to treatment HI: 4 events probably related to treatment
Jacobs <i>et al.</i> , 1997 ⁷⁸	ILis+NPH HI+NPH	NR
Janes <i>et al.</i> , ⁷⁹ 1997	ILis HI	NR
Jansson <i>et al.</i> , 1998 ⁸⁰	ILis+NPH HI+NPH	NR
Johansson <i>et al.</i> , 2000 ⁸¹	ILis+basal HI+basal	NR
Kotsanos <i>et al.</i> , 1997 ³⁹	ILis HI	NR
Linkeschova <i>et al.</i> , 2003 ⁸²	ILis HI	NR

Mathiesen ²² 2007 (new)	IAsp+NPH HI+NPH	Maternal safety profiles and pregnancy outcomes were similar between treatments Adverse events profile was similar in between two arms. Most AEs were mild or moderate and considered unlikely to be related to study products. 18 serious (IAsp, 6; HI, 12) were considered to have a possible relation to study medication. (Caesarean section [IAsp, 1; HI 0], abortion [IAsp, 2; HI, 0]. The frequency and profile of obstetric complications were similar between treatments. The most frequent complications were preeclampsia (IAsp, 13, HI, 11), Threatened preterm labour (IAsp, 6; HI, 7), prolonged labour (IAsp, 5; HI, 7) and unplanned caesarean section (IAsp, 20; HI, 19).
Melki, ⁸³ 1998	ILis+basal HI+basal	Insulin precipitation in the catheter (1x with ILis, 4x with HI); other catheter obstructions (9x with ILis, 9x with HI); small weight gain with both treatments
Persson, ⁸⁴ 2002	ILis+NPH HI+NPH	Retinopathy progression occurred in 3 of 16 patients for ILis and 6 of 17 patients for HI
Provenzano, ⁸⁵ 2001	ILis+basal HI+basal	ILis group: weight loss and decreased appetite, CPK increase, inorganic phosphate increase, and muscle pain HI group: hyperglycemia, hypoglycemia unawareness and flu syndrome.
Raskin, ⁸⁷ 2001	ILis+basal HI+basal	ILis group had one patient hospitalized for ketosis. AEs in HI group were hospitalization for fever, vomiting and dehydration in one patient. Both groups had hyperglycemic episodes and both groups experienced approximately 1kg weight gain per patient. ILis: 16 episodes in 8 patients of hyperglycemia due to occlusion (CSII) HI: 23 episodes in 12 patients of hyperglycemia due to occlusion (CSII)
Raskin, ⁸⁶ 2000	IAsp+NPH HI+NPH	Most common AEs were upper respiratory tract infections, headaches, and accidental injuries. Most of these were mild in severity and not considered to be related to treatment. Four patients in IAsp group reported weight gain, accidental injury, pruritus, and hyperglycemia that were mild in severity but considered to have a possible relationship to the treatment. There was a small increase in BMI after 12 m in both groups.
Recasens <i>et al.</i> , 2003 ⁸⁸	ILis+NPH HI+NPH	NR
Renner, ⁸⁹ 1999	ILis+basal HI+basal	AEs reported by both groups were infections (mainly common cold) and rhinitis, ketosis, injection site reactions, and catheter occlusions. ILis: 1 serious, considered unrelated to treatment HI: 6 serious, considered unrelated to treatment
Roach <i>et al.</i> , 1999 ⁴⁸	ILis Mix50 (a.m.)+I Lis Mix25 (p.m.) BHI50 (a.m.)+BHI30 (p.m.)	AEs: No significant difference between treatments
Schmauss, ⁴² 1998	ILis+basal HI+basal	No severe AEs were registered
Tamás, ⁵⁷ 2001	IAsp+NPH HI	Serious AEs in IAsp group included asthenia, suicide attempt, and pneumonia. Serious AEs in HI group included gastro-enteritis, angina pectoris, carcinoma, and varicose vein. The majority of these (>90%) were deemed by investigators to be unrelated to treatment. The most frequent AE with possible relation to treatment was headache. IAsp: Serious: 6 events (including hypoglycemia) in 5 patients; Non-serious: 314 events in 120 patients HI: Serious: 5 events (including hypoglycemia) in 5 patients; Non-serious: 319 events in 129 patients

Tubiana-Rufi, ⁵⁸ 2004	ILis+basal HI+basal	Minor cutaneous reaction at infusion sites (allergy suspected but not confirmed) during ILis arm in one patient.
Tupola <i>et al.</i> , 2001 ⁴³	ILis+NPH HI+NPH	NR
Valle <i>et al.</i> , 2001 ⁵⁹	ILis+NPH HI+NPH	NR
Vignati <i>et al.</i> , 1997 ⁴⁴	ILis+NPH HI+NPH	No significant differences in the number of treatment- or diseased-related adverse events for the two treatment groups.
Zinman, ⁴⁵ 1997	ILis+basal HI+basal	AEs reported were mild skin reactions at the injection site with both treatments

a.m.=morning; b.i.d.=twice a day; AE=adverse event; BMI=body mass index; CNS=central nervous system; DM=diabetes mellitus; HI=conventional human insulin; IAsp=insulin aspart; ILis=insulin lispro; Mix=premixed (biphasic) insulin; NPH=neutral protamine Hagedorn; NR=not reported; NS=not significant; q.d.=every day; RCTs=randomized controlled trials; SAE=serious adverse event; TEAE = treatment emergent adverse events; UL=ultralente insulin.

*Citations of the studies are listed in the main article, available at www.cmaj.ca/cgi/content/full/180/4/385.