UNIVERSITY OF BIRMINGHAM

Literature search on incidence of seizures associated with hypoglycaemic and hyperglycaemic episodes

Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration

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For the Drivers Medical Group
DVLA
Swansea

ARIF

WMHTAC
West Midlands HTA Collaboration

About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

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Warning

This is a confidential document.

Do not quote without first seeking permission of the DVLA and ARIF.

The information in this report is primarily designed to give approved readers a starting point to consider research evidence in a particular area. Readers should not use the comments made in isolation and should have read the literature suggested. This report stems from a specific request for information, as such utilisation of the report outside of this context should not be undertaken. Readers should also be aware that more appropriate reviews or information might have become available since this report was compiled.

1 Aims

The aims of this report were to address the following questions submitted by the Driver Medical Group:

1.1 Primary Questions

What is the risk and/or incidence of seizures associated with hypoglycaemic episodes in patients with insulin or sulphonylurea treated diabetes?

What is the risk and/or incidence of seizures associated with hyperglycaemic episodes in patients with insulin or sulphonylurea treated diabetes?

1.2 Secondary Questions

At what point (if any) can low blood glucose level be reliably attributed to provoking seizures in patients with insulin or sulphonylurea treated diabetes?

At what point (if any) can high blood glucose levels be reliably attributed to provoking seizures in patients with insulin or sulphonylurea treated diabetes?

Further details are given in the request submitted by the Drivers Medical Group (Appendix 1 – Details of the request

2 Background

The Diabetes Driver Medical Group Panel are currently reviewing the licensing guidelines on seizures during hypoglycaemic and hyperglycaemic episodes.

Background information is given in the documentation supplied by the Drivers Medical Group contained in Appendix 1 – Details of the request.

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycaemia (fasting plasma glucose ≥7.0mmol/l, or two hour 75g oral glucose load plasma glucose ≥11.1mmol/l, on two or more occasions). Acute complications of diabetes include hyperglycaemia with ketoacidosis hyperosmolar syndrome (typical in type 1 diabetics) or non-ketotic hyperosmolar syndrome (typical in type 2 diabetics) which can result in seizures, coma and death. Long-term complications of diabetes include retinopathy, nephropathy, neuropathy and increased risk of atheroma affecting large vessels.[1]

Good glycaemic control in diabetes prevents the acute hyperglycaemic complications and reduces the risk of long-term complications of hyperglycaemia. Hence the goal in the management of diabetes is to achieve blood glucose levels as near normal as possible, with current guidelines recommending that treatment should aim to achieve a blood level of glycated haemoglobin (HbA1c) of between 6.5% and 7.5%.[2,3]

Unfortunately, achieving euglycaemia is difficult due to the increased risk of hypoglycaemia which can be as serious as hyperglycaemia. Symptoms of hypoglycaemia can range from anxiety, palpitations, tremor, sweating and hunger to neurological impairments such as cognitive dysfunction, seizures and coma.[4] The rates of severe hypoglycaemia are more common in type 1 diabetes than type 2 diabetes, with 27% of patients with intensively treated type 1 diabetes in the Diabetes Control and Complications Trial experiencing severe hypoglycaemia compared to 2% of type 2 diabetics in the UK Prospective Diabetes Study.[5,6]

3 Methods

Outline methods were submitted to the Drivers Medical Group by email and acceptance subsequently confirmed by telephone and e-mail (Appendix 2 – Outline methods).

Briefly these were:

- To undertake a search for studies looking at the incidence/risk of seizures during hypoglycaemic or hyperglycaemic episodes in adults with insulin treated or sulphonylurea treated diabetes mellitus
- To initially search for existing systematic reviews
- To concentrate on primary studies (preferably cohort studies) in the absence of systematic reviews
- To comment on the methodological quality of such studies
- To extract and tabulate relevant outcomes and study design characteristics

3.1 Searches

3.1.1 Existing Reviews

Searches to identify existing systematic reviews on this topic were performed utilising the well-established ARIF search protocol (Appendix 3 – Search strategies).

3.1.2 Primary Studies

Searches were undertaken for primary studies in MEDLINE, EMBASE, CINAHL and the Cochrane Library. The search strategy employed MeSH headings and text terms for hypoglycaemia, hyperglycaemia or diabetes with MeSH headings and text terms for seizure. The strategy was developed iteratively and modified accordingly.

The detailed search strategies can be found in Appendix 3 – Search strategies.

Searches were predominantly undertaken by an information specialist with additional searches by a research reviewer. Both interacted to ensure searches were conducted appropriately.

The research reviewer scanned the search results for relevance based on information in the title and abstract. Articles that adhered to the following broad criteria were obtained in full for further scrutiny:

Risk and/or incidence of seizures associated with hypo/hyperglycaemic episodes

Design:	Systematic reviews, cohort studies or cross-sectional studies
Population:	Insulin or sulphonylurea treated type 1 or type 2 diabetes
Exposure:	Hypoglycaemia or hyperglycaemia
Outcome:	Risk of seizures
	Incidence of seizures
Exclusion:	Case reports
	Case series
	Case-control studies
	Studies reporting on mainly children, non-diabetics or type 2 diabetics not treated by sulphonylurea or insulin

Point at which low/high blood glucose levels can be reliably attributed to provoking seizures

Design:	Systematic reviews, cohort studies, case-control studies or case series
Population:	Insulin or sulphonylurea treated type 1 or type 2 diabetes
Exposure:	Hypoglycaemic or hyperglycaemic induced seizures
Outcome:	Blood glucose levels
	Glycosylated haemoglobin levels
Exclusion:	Case series with less than or equal to five patients
	Studies reporting on mainly children, non-diabetics or type 2 diabetics not treated by sulphonylurea or insulin

Full copy articles were assessed for their match to the questions being addressed (external validity) and the most informative articles (most robust study design, large sample size and longest follow-up) subjected to further scrutiny and reporting.

The reference lists of the most relevant articles were also checked in order to identify further relevant papers. A clinical expert was contacted for information on additional studies considered relevant to this report.

3.1.3 Driving Specific Literature

Ad hoc internet searches were conducted to identify relevant driving specific literature using data sources such as the National Transport Laboratory (TRIS), Transport Research Laboratory (TRL) and the Highways Agency.

4 Results

The searches retrieved around 1000 articles. The titles and abstracts were scanned and 20 articles were thought to be relevant and were requested in full. On checking the reference lists of these articles, a further 14 relevant articles were identified and requested in full. From these 34 articles, 8 studies[7-14] were thought to offer the best evidence and these have formed the basis of the report. The majority of the evidence is centred around the frequency of seizures during hypoglycaemic episodes in type 1 diabetics.

Contact was also made with an expert in the field, Professor Brian Frier, who recommended conducting an additional literature search for studies using electroencephalograms and glucose clamping techniques to assess changes in electrical activity in the brain at different blood glucose levels. The search retrieved 5 articles, of which 2 studies[15,16] were thought to be relevant and were requested in full. In addition, Professor Frier provided details on a further 7 studies and 4 of these were requested in full.[17-20] From these 6 studies assessed in full, five studies were excluded; one was conducted on non-diabetic subjects[16] and four studies were conducted on diabetic children.[15,17,18,20] A further two relevant studies were identified from citation checking.[21,22]

The studies cited by the DVLA in the ARIF request form (see Appendix 1 – Details of the request) were not included in the report as they were either case series or conducted in the wrong population. This report is therefore based on the 11 relevant studies mentioned above.[7-14,19,21,22]

4.1 Risk/incidence of seizures in hypoglycaemia

Where possible the risk that a patient with diabetes will experience a seizure during a severe hypoglycaemic episode was calculated (i.e. number of patients experiencing a seizure during a severe hypoglycaemic episode divided by the total number of patients in the study) and the risk of having a seizure during a hypoglycaemic episode was calculated (i.e. number of episodes of seizures divided by total number of severe hypoglycaemic episodes).

4.1.1 Cohort studies

Large prospective cohort studies with long follow-up periods and regular patient assessments offer the best form of evidence for reliably assessing the risk/incidence of events in a defined group of patients. Only one such relevant study was identified.[7] This study assessed the frequency, severity and morbidity of hypoglycaemia in 243 employed people with insulin-treated diabetes in Edinburgh over a 12-month period.

The study was generally well conducted and found that seizures occurred in 21 out of the 238 reported severe hypoglycaemic episodes (defined as requiring treatment by another person and associated either with a blood glucose concentration of <2.8mmol/l or with prompt recovery after administration of oral carbohydrate or the parenteral administration of dextrose or glucagon). Therefore the risk of having a seizure during a severe hypoglycaemic episode is equal to 0.09. See Table 1 for study characteristics and results.

The authors state that 83 participants reported suffering from at least one severe hypoglycaemic episode, but they do not report how many participants suffered a seizure so risk of an insulin-treated diabetic experiencing a seizure cannot be estimated. Glycosylated haemoglobin levels were recorded at 6 monthly intervals and blood glucose levels were recorded if measured at the time of hypoglycaemia, but associations between these variables and the risk of seizure were not explored.

It should be noted that the study was conducted in employed people, therefore the results may not be generalisable to the insulin-treated diabetic population as employed people may be healthier on average as they are able to work. Therefore the frequency of episodes of seizures reported in the study maybe lower than expected.

4.1.2 Cross-sectional studies

Five relevant cross-sectional studies were identified with sample sizes ranging from 158 to 1076 participants.[8-12] Each study required participants to recall the frequency and severity of hypoglycaemic episodes in the preceding year or in the case of one study in the preceding week. The majority of the studies were conducted in Europe on type 1 diabetics attending diabetes outpatient clinics (see Table 1 for study characteristics and results). The study populations were comparable (e.g. with regards to insulin regimens), however, it is still difficult to compare the results of the studies due to differences in reported outcomes.

Some studies report only the number of episodes of severe hypoglycaemia with seizure, but not the number of patients experiencing the event, therefore it is not possible to determine whether this represents a small number of patients experiencing more than one seizure or a large number of patients experiencing one seizure. Equally, some studies only report the number of patients experiencing a seizure during a hypoglycaemic episode and not the frequency of episodes of seizures. A further difficulty arises in that the majority of studies identified report the number of severe hypoglycaemic episodes with coma and/or seizure as a single outcome. Therefore, it was not possible to determine the frequency of seizures as some episodes would have involved coma without seizure. Furthermore, different definitions of severe hypoglycaemia used in the studies, render comparisons of risk of seizure during hypoglycaemia between studies difficult.

The studies were well conducted with minimal response and sampling bias and no generalisability issues. However all the studies will have been subjected to recall bias as participants had to remember the frequency and details of hypoglycaemic episodes and most studies used the preceding year as the time frame. Only one study had shorter time frames.[10] In this study, subjects were asked to prospectively record the frequency and severity of hypoglycaemic episodes through diary keeping over a week and also retrospectively recall the frequency and severity of hypoglycaemic episodes in the preceding week through a questionnaire. No significant difference between the prospectively collected results and the retrospectively results was found, suggesting that subjects accurately recalled information over a period of a week.

Only two studies, Macleod et al[8] and Pramming et al[10] report the frequency of seizures during hypoglycaemic episodes, enabling the risk of a type 1 diabetic experiencing a seizure during a severe hypoglycaemic episode to be calculated (i.e. number of patients experiencing a seizure divided by the total number of

patients in the study). The remaining three studies report the frequency of seizures or coma during hypoglycaemic episodes as a single outcome.

Macleod et al state that 5 out of 302 patients with insulin treated diabetes (majority type 1 diabetics) reported experiencing seizures during hypoglycaemia in the preceding year, which gives a 0.02 risk of an insulin treated diabetic experiencing a seizure during a hypoglycaemic episode in a year. Pramming et al state that 1 out of 411 patients with type 1 diabetes reported experiencing one episode of seizure during hypoglycaemia in the preceding week. Therefore the risk of a type 1 diabetic experiencing a hypoglycaemic episode with seizure in a week is equal to 0.002, which gives a risk of having a seizure in a year of 0.12.[*] These risks cannot be compared to the cohort study conducted by Leckie et al discussed above, as Leckie et al only report the number of episodes of seizures, not the number of patients experiencing seizures.

Two of the cross-sectional studies identified report the frequency of seizures or coma during hypoglycaemia as a single outcome and one study reports the frequency of coma, seizure, or treatment with glucagon or intravenous dextrose as a single outcome.[9,11,12] These results have been extracted (see Table 1) and are discussed below. However the results should be treated with caution as they will include episodes of coma only.

The largest study (Pedersen-Bjergaard et al[9]) of 1076 participants with type 1 diabetes, conducted in England and Denmark reports a rate of severe hypoglycaemia in the preceding year equal to 1.3 episode/patient/year and a rate of severe hypoglycaemia with coma or seizures equal to 0.35 episodes/patient/year which gives a risk of experiencing a seizure or coma during a severe hypoglycaemic episode of 0.27. It is not possible to estimate the risk of a type 1 diabetic having a seizure as the number of patients who had a seizure is not reported, only the number of episodes.

Ter Braak et al[11] conducted a cross-sectional study on 195 type 1 diabetics in the Netherlands and amongst other outcomes, assessed the frequency of severe hypoglycaemic episodes complicated by hypoglycaemic coma, seizure, or treatment with glucagon or intravenous dextrose. They found the risk of a type 1 diabetic experiencing a hypoglycaemic episode complicated by coma, seizure, or treatment with glucagon or intravenous dextrose in the preceding year to be 0.19 and the risk of experiencing coma, seizure, or treatment with glucagon or intravenous dextrose during a severe hypoglycaemic episode in the preceding year to be 0.46.

Ward et al[12] conducted a cross-sectional study on 158 insulin dependent diabetics (including a small number of type 2 diabetics) in New Zealand. They report 27 subjects experiencing coma or convulsions during a hypoglycaemic episode in the preceding year, with four patients experiencing greater than 4 episodes of coma or convulsions during a hypoglycaemic episode in the preceding year. Therefore the risk of an insulin dependent diabetic experiencing coma or convulsions during a hypoglycaemic episode over a year was calculated to be 0.17.

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[*] $1-((1-1/411)^{52})$

4.2 Blood glucose level at which hypoglycaemia can be reliably attributed to seizure

None of the studies retrieved from the literature search directly addressed blood glucose levels at which hypoglycaemia can be reliably attributed to seizure(s). The additional literature search and the recommended studies by Professor Brian Frier, looking at electroencephalogram measurements which mirror the function of the brain during glucose clamping, retrieved one relevant study conducted by Pramming et al.[19] Citation checking identified a further two relevant studies (Bendston et al[22] and Tallroth et al[21]).

The study by Pramming et al[19] was well conducted and assessed the effect of hypoglycaemia on brain function in 13 patients with insulin dependent diabetes. A gradual fall in blood glucose was induced by a bolus injection of insulin followed by an intravenous infusion of insulin. During 60 minutes of hypoglycaemia and after restoration of euglycaemia with intravenous glucose, electroencephalograms were evaluated continuously and blood glucose levels were taken every 10 minutes. The median blood glucose concentrations immediately before the appearance of significant changes in the electroencephalogram was 2.3 (95% CI 2.0 – 2.6)mmol/l and the median glucose concentrations immediately after the appearance of significant changes in the electroencephalogram was 1.9 (95% CI 1.4-2.1)mmol/l. A normal electroencephalogram was established at 2.0 (95% CI 1.8 – 2.1)mmol/l. One patient did not show any electroencephalogram changes.

Although the observed changes in the electroencephalogram measurements are not proven to be associated with the occurrence of seizures, it is clear that hypoglycaemia causes changes in the cortex at a narrow range of blood glucose concentration in insulin-dependent diabetics. A non-diabetic control group was not assessed in this study.

Tallroth et al[21] assessed electroencephalogram and P300 recordings before, during and immediately after hypoglycaemia induced by intravenous infusion of regular insulin in eight cases (patients with type 1 diabetes) and in twelve controls (age-matched healthy male participants). Hypoglycaemia produced a significant increase in low frequency electroencephalographic activity in both groups and was most pronounced over anterior regions of the brain. The electroencephalographic activity was normalised immediately after the hypoglycaemic period in both groups. The diabetes group showed longer P300 latencies during the initial euglycaemic period. Hypoglycaemia caused a marked reduction of the P300 amplitude in both groups and the amplitude was not restored immediately after normalisation of blood glucose levels.

Bendtson et al[22] studied eight type 1 diabetic patients overnight for two consecutive and one subsequent night with continuous monitoring of electroencephalogram. All the patients experienced insulin-induced hypoglycaemia with a blood glucose nadir of 1.6 (range 1.4-1.9)mmol/l and blood glucose concentrations correlated to the rank of individual electroencephalogram-patterns during the whole night. Three of the eight patients showed electroencephalogram changes at blood glucose levels below 2.0 (1.6-2.0)mmol/l. The changes were found equally in all regions of the brain. The three patients with electroencephalogram

changes during nocturnal hypoglycaemia could only be separated from the other five patients by their impaired glucagon responses.

4.3 Risk/incidence of seizures in hyperglycaemia

None of the studies retrieved from the literature search addressed the risk/incidence of seizures in hyperglycaemic diabetic patients. Only case reports, case series and case-control studies were found. These types of studies cannot be used to estimate the risk/incidence of seizures in hyperglycaemic diabetics as only diabetics suffering seizures due to hyperglycaemia will be recruited into the study making it impossible to determine risk/incidence of seizures.

Although not related to the questions addressed by the DVLA, it was observed that the majority of case reports and case series on seizures in hyperglycaemic diabetic patients included type 2 diabetics with non-ketotic hyperglycaemia implying that seizures may be more common in non-ketotic hyperglycaemia than ketoacidosis hyperglycaemia. A case-control study conducted in the United States that may be of interest,[13] addressed this question by reviewing the medical records of 51 cases (diabetics presenting with seizures) and 119 controls (random sample of diabetics presenting with a variety of medical and surgical problems). They found that diabetics presenting with seizures were four times more likely to be non-ketotic than ketotic (Odds Ratio = 4.03, 95% CI 1.76-9.24, p-value = 0.001). The study also details the types of seizures experienced by the seizure group which may be of interest to the panel. However these results should be interpreted with caution as the study contains limited information on methods and patient characteristics so it is difficult to determine whether any biases may have been introduced and what population the results are generalisable to.

4.4 Blood glucose level at which hyperglycaemia can be reliably attributed to seizure

Two case-control studies that assessed the association between blood glucose levels and occurrence of seizures in type 1 and type 2 diabetics were identified.[13,14] Gao et al,[13] mentioned earlier in the report, reviewed the medical records of 51 cases (type 1 and 2 diabetics presenting with seizures) and 119 controls (random sample of type 1 and 2 diabetics presenting with a variety of medical and surgical problems). The study found no significant differences in serum levels of glucose between the control group and seizure group. However no information is disclosed on the time of blood glucose measurements, other than that they were extracted from medical notes and it is unlikely that they will have been measured at time of seizures.

Sabitha et al[14] conducted a case-control study in 40 cases (patients presenting with first time seizures who were detected to be diabetic and hyperglycaemic) and 40 controls (euglycaemic patients with first episode of seizure and CT scan showing infarct). They report a statistically significant correlation between the frequency of seizures and blood glucose levels (r = 0.671) and a statistically significant correlation between the duration of seizures and blood glucose levels (r= 0.845). However the results of the study are poorly reported and it is not clear if these results are based on the whole study group (80 participants) or only on the cases. Also it is not clear whether these results are applicable to the UK population as the study is

conducted in an Indian population and no information is given on the participants' treatment regimen which may not be comparable to that in the UK.

Both studies are poorly reported with limited information on methods and patient characteristics so it is difficult to determine whether any biases may have been introduced and to what population the results are applicable to. However, recording biases inherent in studies using medical records for outcome data are likely to be reduced in these studies as the cases and controls are both inpatients therefore the medical records for both groups are likely to be comparable.

4.5 Driving perspective

None of the studies identified assessed the frequency of drivers with diabetes experiencing seizures during hypo/hyperglycaemia or the frequency of accidents in drivers with diabetes due to seizures during hypo/hyperglycaemia.

An interesting review of the evidence on the influence of chronic illness and impairments on crash involvement of motor vehicle drivers was identified,[23] which commented on a study of some relevance.[24] The study by Songer et al asked 428 subjects with type 1 diabetes in the US to recall frequency and severity of hypoglycaemic episodes in the preceding year and to recall details of any driving accidents experienced in the previous year. 11% of subjects reported being involved in an accident in the preceding year. Accidents were associated with younger age, greater exposure of driving (miles driven) and frequency of severe hypoglycemia (defined as resulting in loss of consciousness). 32.6% of drivers involved in accidents experienced severe hypoglycaemia compared to 16.9% in those not being involved in accidents ($p<0.02$). Accidents were not associated with mild hypoglycaemia.

5 Conclusion

The majority of the evidence found were cross-sectional studies assessing the frequency of seizures during hypoglycaemic episodes in type 1 diabetics. These studies were generally well conducted, but as with all cross-sectional studies will have been subjected to some recall bias. It was not possible to compare the risk of seizures between the studies due to different definitions of severe hypoglycaemic episodes and differences in the reporting of outcomes related to seizure, e.g. studies reporting either the number of episodes of seizures, the number of patients experiencing seizure, or reporting seizure or coma as a single outcome. The most informative studies suggest risks ranging from 0.02 – 0.12 of a type 1 diabetic having a severe hypoglycaemic episode complicated by seizure in a year. One prospective cohort study was found, which reported the risk of a severely hypoglycaemic type 1 diabetic patient experiencing a seizure of 0.09 over a year.

No studies were found assessing the frequency of seizures in hyper/hypoglycaemic type 2 sulphonylurea treated diabetic patients and hyperglycaemic type 1 and 2 insulin treated patients.

Limited information was found on blood glucose levels that can be reliably associated with seizures. The majority of studies retrieved were of cross-sectional design and hence it was not possible to make

associations between blood glucose levels and occurrence of seizures as blood glucose measurements were unlikely to be recorded at the time of seizure. Studies looking at electroencephalogram changes during hypoglycaemia seem to show that changes in the brain are observed at a narrow range of blood glucose concentration.

5.1 Limitations of this report

This is not a systematic review but a rapid assessment for relevant literature. The literature on hypo/hyperglycaemia is large. Searches were restricted by use of terms for seizure in order to make the task manageable within the resources available for this report. To ensure that relevant studies not captured by the search strategy were not overlooked, contact with experts and citation checking of relevant studies were employed. However some relevant studies may have been missed.

The majority of studies included in the report are of cross-sectional design asking participants to recall previous hypo/hyperglycaemic events over the preceding year. Therefore these studies are likely to have been subjected to recall bias.

Table 1: Risk/frequency of seizures in hypoglycaemia

Study	Design	Size	Population	Relevant outcome	Method of measurement	Results	Comments
Leckie et al[7] 2005	Prospective cohort study with 12-month follow-up, conducted in the UK	243	▪ Employed people with insulin treated diabetes (of which 27 had type 2 diabetes) ▪ Treatment regimen: o 51 (21%) subjects used twice daily insulin therapy in the form of soluble and NPH o 192 (79%) subjects used multiple insulin injections of preprandial soluble or fast-acting insulin analogs with bedtime NPH ▪ Age range: 20-69 years ▪ Mean HBA_{1c}: 9.1% ▪ Impaired awareness of hypoglycaemia: 7 subjects (3%)	Frequency of severe hypoglycaemic episodes (defined as requiring treatment by another person and associated either with a blood glucose concentration of <2.8mmol/l or with prompt recovery after administration of oral carbohydrate or the parenteral administration of dextrose or glucagon) with seizure	Self-completed form for every episode of hypoglycaemia experienced with additional information provided by person who provided assistance during sever episode HBA_{1c} obtained from medical records at baseline, 6 months and 12 months Blood glucose was recorded if it had been measured at the time of the episode	Seizures occurred in 21 of the 238 reported severe hypoglycaemic episodes Therefore risk of seizure during a severe hypoglycaemic episode = 0.09	▪ Sampling bias not likely to have been introduced as all eligible patients approached to participate in study. ▪ Not possible to determine if study was subjected to response bias as all people with insulin-treated diabetes attending the diabetes outpatient clinic at the Royal Infirmary of Edinburgh during 1998-1999 were invited to participate, but it was not known how many were in employment and hence eligible to participate. ▪ High follow-up rate (98%). ▪ Not possible to estimate the risk of a type 1 diabetic having a seizure as no. of patients who had a seizure is not reported, only the number of episodes.
Pedersen-Bjergaard et al[9] 2004	Cross-sectional conducted in the UK & Denmark	1076	▪ Type 1 diabetics attending secondary care clinics in Denmark and England ▪ Median age (range): 40 (18-81) years ▪ Female: 44.5% ▪ Median (range) duration of diabetes: 21 (2-65) years ▪ Median (range) age at onset: 20 (0-40) years ▪ Mean (SD) HbA_{1c}: 8.6% (1.3) ▪ ≥4 insulin injections per day: 71.6% ▪ Mean (SD) insulin dose: 0.66 (0.23) IU/kg ▪ Impaired awareness of hypoglycaemia (self-estimated): 57.6%	▪ Frequency of mild hypoglycaemic events (managed by the patient) in the previous week ▪ Frequency of severe hypoglycaemic events (assistance from others needed to restore blood glucose) in the preceding one and two year periods ▪ Severity of severe hypoglycaemic event according to level of consciousness (coma/seizure or awake)	▪ Self-completed questionnaire	Results based on 1047 patients: ▪ Rate of mild hypoglycaemic episodes = 2 episodes/patient/week Therefore total no. of mild episodes = 2094 ▪ Rate of severe hypoglycaemia in the preceding year = 1.3 episode/patient/year Therefore total no. of severe episodes = 1361 ▪ Rate of severe hypoglycaemia with coma or seizures = 0.35 episodes/patient/year Therefore total no. of coma or seizure = 366 ▪ Risk of coma/seizure during any hypoglycaemic episode (mild/severe) = 0.11 ▪ Risk of coma/seizure during a	▪ Sampling bias not likely to be introduced as all eligible patients attending the participating clinics between 1999-2000 were approached to take part in study. ▪ High response rate of 91%. Non-responders reported to have a slightly higher prevalence of macrovascular complications, therefore response bias may have been introduced. ▪ Not possible to estimate the risk of a type 1 diabetic having a seizure as no. of patients who had a seizure is not reported, only the number of episodes. ▪ Recall bias

Study	Design	Size	Population	Relevant outcome	Method of measurement	Results	Comments
						severe hypoglycaemic episode = 0.27	
MacLeod et al[8] 1993	Cross-sectional conducted In the UK	600	▪ Diabetics patients treated with insulin (including 56 type 2 diabetics) for more than 1 year and attending the diabetic outpatient clinic at the Royal Infirmary of Edinburgh ▪ Treatment regimen: o 454 (76%) patients used soluble and intermediate-acting insulins which were administered twice daily. o 65 (11%) patients used a basal/bolus regimen of three injections of soluble insulin before meals, supplemented by a single dose of intermediate acting insulin. o 75 (13%) used one daily insulin injection. ▪ Median age (range): 41 (14-79) years ▪ Median duration of diabetes (range): 15 (1-62) years ▪ Median duration of insulin therapy (range): 13 (1-62) years ▪ Median daily insulin dose (range): 0.7 (0.2-2.0) units/kg ▪ Mean HbA_{1c} (range): 10.7% (6.0-16.4)	Measured in first 302 patients recruited: ▪ Frequency of convulsions associated with hypoglycaemia ▪ Frequency of traffic accidents associated with hypoglycaemia Measured in all 600 patients: ▪ Frequency of severe hypoglycaemic events (external assistance to promote recovery) in the preceding year.	▪ Self-completed questionnaire	▪ No. of patients experiencing hypoglycaemic induced convulsions in preceding year = 5 (all type 1 diabetics) ▪ Therefore risk of insulin-treated diabetic experiencing a seizure in a year = 0.02 ▪ No. of patients involved in traffic accidents associated with hypoglycaemia = 5 ▪ Therefore risk of traffic accidents associated with hypoglycaemia in insulin-treated patients = 0.02	▪ Sampling bias not likely to be introduced as patients randomly selected for participation using random number tables. ▪ No response bias as none of the patients declined to participate. ▪ Paper does not report the number of type 2 patients in the 302 subgroup of patients, therefore only risk of seizure in insulin-treated diabetics can be calculated ▪ Paper does not report the frequency of severe hypoglycaemic episode in the 302 subgroup, therefore risk of severely hypoglycaemic insulin-treated diabetic experiencing a seizure can not be calculated. ▪ Recall bias
Pramming et al[10] 1991	Cross-sectional & prospective cohort study conducted in Denmark	411	▪ Type 1 diabetic patients ▪ Median age (range): 37 (15-80) years ▪ Male/Female: 208/203 ▪ Median HBA1c (range): 8.7% (5.6-18.2) ▪ Treatment regimen: o Insulin once daily: 41 patients (10%) o Insulin twice daily: 321 patients (78%) o Insulin thrice daily: 49 patients (12%) o Daily insulin dose>0.5 U/Kg: 181 patients (44%)	▪ Frequency of mild hypoglycaemic events (managed by the patient) in the previous week ▪ Frequency of severe hypoglycaemic events (assistance from others needed) in the preceding week ▪ Frequency of convulsions due to hypoglycaemia	▪ Self-completed questionnaire on the frequency and symptoms of hypoglycaemic episodes in the preceding week and month. ▪ Patients recorded the frequency, severity and symptoms of hypoglycaemic episodes in a	Prospective (diary) recordings: ▪ Frequency of mild hypoglycaemic episodes/week = 724 ▪ No. of patients experiencing mild hypoglycaemic episode(s)/week= 290 ▪ Frequency of severe hypoglycaemic episodes/week = 11 ▪ No. of patients experiencing severe hypoglycaemic episode(s)/week= 11 ▪ No. of patients experiencing convulsions due to hypoglycaemia/week = 1 ▪ Frequency of hypoglycaemic	▪ Sampling bias not likely to be introduced as patients randomly selected for participation. Method of randomisation not stated. ▪ High response rate of 90%, therefore minimal response bias introduced. ▪ Retrospective recordings did not differ significantly from prospective recordings, indicating that recall bias is not an issue.

Study	Design	Size	Population	Relevant outcome	Method of measurement	Results	Comments
					diary for 1 week. ▪ HBA1c measured before and after completing questionnaire and diary.	episodes with convulsion/week = 1 ▪ Therefore risk of type 1 diabetic experiencing a hypoglycaemic episode with seizure in a week = 0.002 ▪ Risk of hypoglycaemic (mild/severe) type 1 diabetic experiencing a seizure in a week = 0.003 ▪ During their diabetic life, 151 (36%) of the patients had been unconscious due to hypoglycaemia. 63 (42%) once, 41 (27%) twice, 33 (22%) from three-ten times and 14 (9%) more than ten times. ▪ Frequency of hypoglycaemic episodes with unconsciousness was significantly correlated with HBA1c (r=-0.19, p<0.05)	
Ter Braak et al[11] 2000	Cross-sectional conducted in the Netherlands	195	▪ Type 1 diabetics ▪ Mean age (SD): 41 (+/-14) years ▪ HbA1c: 7.8% (+/- 1.2) ▪ Diabetes duration: 20 (+/-12) years ▪ Treatment regimen: o Intensive insulin treatment: 160 (82%) patients o Insulin dose/24hr: 0.74 (+/- 0.24) U/kg	▪ Frequency of severe hypoglycaemic episodes (help from others required) during the previous year ▪ Frequency of severe hypoglycaemic complicated by hypoglycaemic coma, seizure, or treatment with glucagon or intravenous dextrose	Self-completed questionnaire	▪ No. of patients experiencing severe hypoglycaemic episode = 81 patients/year ▪ No. of patients experiencing severe hypoglycaemic episode complicated by hypoglycaemic coma, seizure, or treatment with glucagon or intravenous dextrose in previous year = 37 patients/year ▪ Risk of type 1 diabetic experiencing a hypoglycaemic episode complicated by hypoglycaemic coma, seizure, or treatment with glucagon or intravenous dextrose in previous year = 0.19 ▪ Risk of severely hypoglycaemic type 1 diabetic experiencing coma, seizure, or treatment with glucagon or intravenous dextrose in previous year = 0.46	▪ Sampling bias may have been introduced as although consecutive patients visiting clinic during 6 weeks period were approached to take part, as well as non-consenting patients, some eligible patients were excluded and no reasons were given. ▪ High response rate of 92%, therefore minimal response bias introduced. ▪ Recall bias ▪ Rates of severe hypoglycaemic episodes and complicated severe hypoglycaemic episodes are given, but not clear if these are per total study population or per hypoglycaemic population.
Ward et al[12] 1990	Cross-sectional conducted in New Zealand	158	▪ Insulin dependent diabetes (including small no. of type 2 diabetics) ▪ Mean age (range): 44 years (17-78) ▪ Mean duration of insulin therapy: 16 years (1-47) ▪ Treatment regimen: o 1 insulin injection daily: 13	Number of patients experiencing coma or convulsions during hypoglycaemia in preceding year and in lifetime	Self-reported questionnaire	▪ Number of patients experiencing coma or convulsions during hypoglycaemia: o in lifetime = 67 patients o in preceding year =27 patients o of ≥5 episodes in the last year = 4 patients ▪ Therefore risk of insulin dependent diabetic experiencing coma or	▪ Sampling bias not likely to be introduced as patients randomly selected for participation. Method of randomisation not stated. ▪ High response rate of 95%, therefore minimal response bias introduced. ▪ Recall bias

Study	Design	Size	Population	Relevant outcome	Method of measurement	Results	Comments
			(8%) patients o 2 injections daily: 108 (70%) patients o 3 injections daily: 24 (16%) patients o 4 injections daily: 10 (6%) patients			convulsions during hypoglycaemia over a year = 0.17 Driving related results: No of drivers: 128 (81%) patients % of drivers who had not informed DVLA: 69% % of drivers experiencing hypoglycaemia whilst driving: 40% % of drivers who had an accident due to hypoglycaemia: 13%	

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3 National Collaborating Centre for Women's and Children's Health, National Collaborating Centre for Chronic Conditions. NICE clinical guidelines on type 1 diabetes in children, young people and adults. URL: http://www.nice.org.uk/guidance/CG15/niceguidance/pdf/English
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7 Appendices

7.1 Appendix 1 – Details of Request

ARIF REQUEST FORM

Date of request: 23/11/2006

Lead Medical Adviser issuing request:

Name – Dr Simon Rees
Secretary to the Diabetes Panel

Contact details:

Drivers Medical Group
DVLA
Sandringham Park
Swansea Vale
Llansamlet
Swansea
SA7 0AA

[redacted]

[redacted]

1. Without worrying about the structure of the question, state in full the nature and context of the problem.

We need to know the risk and incidence of seizure associated with hyperglycaemic and hypoglycaemic episodes with evidence of blood glucose recordings if possible. We would need to decide at what (if any) blood glucose reading we would accept seizures as provoked for both hypoglycaemia and hyperglycaemia.

2. Please give a background to the question. Why has DMG raised this problem?

DVLA have always treated drivers who experience a hypoglycaemic attack with seizure as being provoked and not having any driving implication. This is in contrast to alcohol and drug associated fits requiring 12 months off driving.

We have recently been made aware of a case in which it was suggested that the cause of a seizure was **hyper**glycaemia. In this particular case no blood glucose recording was available and it was treated by DVLA as a solitary seizure.

3. Giving references where appropriate, briefly detail the sources you have used to obtain background information on the *options* and *issues,* which might be important for the problems, you describe.

(a) Chapter 3 Diabetes Mellitus – At a Glance guide to the current Medical Standards of Fitness to Drive February 2006

(b) Fisher B M, Frier B M Nocturnal convulsions and insulin-induced hypoglycaemia in diabetic patients. *Postgraduate Medical Journal (1987) 63, 673-676*

(c) Hart S P, Frier B M Causes, management and morbidity of acute hypoglycaemia in adults requiring hospital admission. *Q J Med 1998; 91: 505-510*

(d) Tiamkao S et al Seizures in nonketotic hyperglycaemia. *Seizure 2003; 12: 409-410*

(e) Grant C, Warlow C Focal epilepsy in diabetic non-ketotic hyperglycaemia. *British Medical Journal, 1985;Volume 290*

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(g) Hennis A, Corbin D, Fraser H Focal seizures and non-ketotic hyperglycaemia. *Journal of Neurology, Neurosurgery and Psychiatry 1992; 55: 195-197*

4. Please give name and contact details of any expert or clinical contact e.g. relevant Panel Chairman/expert Panel member.

Professor Brian M Frier (Chairman)
BSc Ed MD FRCP
Consultant Physician and Diabetologist
Department of Diabetes
Royal Infirmary of Edinburgh
51 Little France Crescent
Edinburgh EH16 4SA

[redacted]

5. What is the nature of the target population of the issue detailed above? Eg. age profile, vocational drivers, young drivers, other co-morbid features.

Group 1 (ordinary driving licence - car) drivers of all ages.
Drivers with insulin-treated diabetes
Drivers with diabetes treated with sulphonylurea

6. What are the outcomes you consider particularly important in relation to the question posed? What decisions rest on these outcomes?

Fitness for Group 1 licensing

7. What is the latest date that an ARIF response would be of value 31 / 01 /2007

Please either:

Fax this form to: 0121 414 7878 marking FAO ARIF

E-mail as a word document or pdf attachment to: [redacted]

Post to: -
Dr David Moore
Senior Research Reviewer and Analyst
Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration
Department of Public Health
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Please ring 0121 414 3166 or 6769 if you have any queries, or you want to check the progress with your request.

7.2 Appendix 2 – Outline methods

- To determine:
    - The risk and/or incidence of seizures associated with hypoglycaemic episodes
    - The risk and/or incidence of seizures associates with hyperglycaemic episodes
    - The point (if any) at which low blood glucose levels can be reliably attributed to provoking seizures
    - The point (if any) at which high blood glucose levels can be reliably attributed to provoking seizures

  in adults with insulin treated or sulphonylurea treated diabetes mellitus
- MEDLINE (Ovid) (1966-2006), EMBASE (Ovid) (1980-2006) and the Cochrane Library (Wiley) (2006 Issue 4) and other relevant databases will be searched using a comprehensive search strategy
- The identified articles will be screened by an analyst for relevance
- Systematic reviews and primary studies (preferably cohort studies) that report the relevant outcomes (e.g. risk/incidence of seizures) will be selected and the most robust, with regards to study design and sample size, will be commented upon
- Methodological quality of these studies will be discussed
- Data on relevant outcomes will be extracted and reported

7.3 Appendix 3 – Search strategies

7.3.1 ARIF Reviews Protocol

SEARCH PROTOCOL FOR ARIF ENQUIRIES

(Oct 2006)

In the first instance the focus of ARIF's response to requests is to identify systematic reviews of research. The following will generally be searched, with the addition of any specialist sources as appropriate to the request.

1. Cochrane Library

- Cochrane Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database

An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD

- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments and Evidence Based guidelines

- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes, Public Health excellence
- SBU – Swedish Council on Technology Assessment in Health Care
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Agency for Drugs and Technologies in Health
- New Zealand Health Technology Assessment
- STEER Reports (no longer published)
- Agency for Healthcare Research and Quality (AHRQ)
- Alberta Heritage Foundation
- McGill Medicine Technology Assessment Unit of MUHC (McGill University Health Centre)
- Monash reports – Centre for Clinical Effectiveness, Monash University
- US Department of Veterans Affairs
- NHS QIS (Quality Improvement Scotland)
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases

- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts

- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products.

7.3.2 Primary Studies Search Strategies

Database: Cochrane Library (Wiley) 2006 Issue 4
Strategy 1:

ID	Search
#1	diabet* in All Fields in all products
#2	blood near/2 sugar* in All Fields in all products
#3	blood near glucose* in All Fields in all products
#4	hyperglyc* or hypoglyc*
#5	MeSH descriptor Glucose Metabolism Disorders explode all trees
#6	(#1 OR #2 OR #3 OR #4 OR #5)
#7	seizure*
#8	convulsion*
#9	MeSH descriptor Seizures explode all trees
#10	(#7 OR #8 OR #9)
#11	(#6 AND #10)
#12	incidence
#13	occurrence
#14	risk
#15	(#12 OR #13 OR #14)
#16	(#11 AND #15)

Search Strategy 2:

#1	hyperglyc* or hypoglyc*
#2	MeSH descriptor Hyperglycemia explode all trees
#3	MeSH descriptor Hypoglycemia explode all trees
#4	(#1 OR #2 OR #3)
#5	seizure* or conscious* or fit* or convulsion* or reaction*
#6	(#4 AND #5)
#7	MeSH descriptor Diabetes Mellitus explode all trees
#8	(#4 OR #7)
#9	(#8 AND #5)
#10	seizure*:ti or convulsion*:ti. or fit*:ti. or conscious* or reaction*:ti. or epilept*:ti. or driv*:ti.
#11	(#8 AND #10)
#12	fitness near drive
#13	(#11 OR #12)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 07, 2006>
Search Strategy:

1 seizure$.mp.
2 convulsion$.mp.
3 or/1-2
4 incidence.mp.
5 occurrence.mp.
6 occurr$.mp.
7 or/4-6
8 diabetic$.mp.
9 diabetes.mp.
10 hyperglyc$.mp.
11 hypoglyc$.mp.
12 or/8-11
13 3 and 7 and 12
14 3 and 12

Database: Ovid MEDLINE(R) <1966 to November Week 3 2006>
Search Strategy:

1 exp Hyperglycemia/ or hyperglycaemia.mp.
2 hyperglycemia.mp.
3 exp Hypoglycemia/ or hypoglycaemia.mp.
4 hypoglycemia.mp.
5 hypergly$.mp.
6 hypogly$.tw.
7 or/1-6
8 diabetes.mp. or Diabetes Mellitus, Type 2/ or exp Diabetes Mellitus/
9 diabetic$.mp.
10 exp Diabetes Mellitus/
11 or/8-10
12 seizure$.ti.
13 convulsion$.ti.
14 fit$.ti.
15 conscious$.ti.
16 reaction$.ti.
17 or/12-16
18 7 or 11
19 17 and 18
20 limit 19 to ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")

Database: EMBASE <1980 to 2006 Week 52>
Search Strategy:

1 hypergl$.tw.
2 hypogl$.tw.
3 exp Hyperglycemia/
4 exp Hypoglycemia/
5 exp Diabetes Mellitus/
6 seizure$.ti.
7 convulsion$.ti.
8 fit$.ti.
9 reaction$.ti.
10 conscious$.ti.
11 or/6-10
12 or/1-5
13 12 and 11
14 limit 13 to (adult <18 to 64 years> or aged <65+ years>)

Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to December Week 2 2006>
Search Strategy:

1 hypergl$.tw.
2 hypogl$.tw.
3 exp Hyperglycemia/
4 or/1-3
5 exp Diabetes Mellitus/
6 4 or 5
7 incidence.mp. or INCIDENCE/
8 occurr$.mp.
9 or/7-8
10 convulsion$.mp. or exp Convulsions/
11 fit$.mp.
12 reaction$.mp.
13 seizure$.mp. or exp Seizures/
14 conscious$.mp.
15 or/10-14
16 15 and 6 and 9
17 limit 16 to (adult <19 to 44 years> or middle age <45 to 64 years> or aged <65 to 79 years> or "aged <80 and over>")

Other databases/sites searched (15/12/2006):

National Research Register
ClinicalTrials.gov
TRIS Online (National Transportation Library)
TRL (Tranportation Research Laboratory)
UNESCO
Highways Agency
CARE Europe
US Driving Assessment Symposia
Monash University Accident Research Centre
NHTSA (National Highway Traffic Safety Association)
National Centre for Statistics and Analysis (NHTSA)
NZ Fitness to Drive
Driving Assessment 2001, 2003 and 2005 International Driving Symposia on Human Factors in Driver Assessment, Training and Vehicle Design Various locations

Search terms used: hyperglycaem*, hypoglycaem*, hyperglycem*, hypoglycem*, diabetes, blood sugar, seizure*, convulsion*, conscious*, driver*, driving, fitness to drive