HYPOAWARE

A psychoeducational group intervention for people with type 1 and insulin-treated type 2 diabetes and problematic hypoglycaemia

In persons with type 1 and type 2 diabetes severe hypoglycaemia, defined as a low blood glucose where there is a need of external assistance due to confusion or loss of consciousness, is one of the most impactful adverse events associated with insulin treatment. Severe hypoglycaemia can lead to significant morbidity, fear of hypoglycaemia, reduced quality of life, and even death as well as to high societal costs in terms of increased health care consumption and reduced work productivity. Episodes of severe hypoglycaemia occur in 30-37% of people with type 1 diabetes. The estimated incidence ranges from 1.0 to 1.7 episodes per patient per year and can grow to up to 3.2 episodes per patient per year in persons with a longer disease duration. In people with type 2 diabetes with progressive insulin deficiency, frequency of severe hypoglycaemia approaches that of type 1 diabetes. A 25-fold increased risk of severe hypoglycaemia is associated with hypoglycaemia-associated autonomic failure. This comprises a defect in hormonal counter regulation and impaired awareness of symptoms of hypoglycaemia. There is also evidence that psychobehavioural factors, like inattention for symptoms of hypoglycaemia, misinterpretation and the postponement of corrective measures, are at least partly responsible for an increased risk of severe hypoglycaemia.

Chapter 2 is a systematic review and meta-analysis of studies investigating the effects of psychoeducational interventions in persons with diabetes and problematic hypoglycaemia. We searched medical databases up to 19 October 2015 and included three randomised controlled trials on Blood Glucose Awareness Training (BGAT)-based interventions, all aimed at reducing the burden of hypoglycaemia, in the meta-analysis. Data of 317 adults with type 1 diabetes and problematic hypoglycaemia could be summarized.

The psychoeducational interventions reduced episodes of severe hypoglycaemia (mean difference (MD): −1.03 episodes per 6 months [−1.69, -0.37]; P = 0.002), increased the hypoglycaemia symptom blood glucose threshold (MD: 0.17 mmol/L [0.02, 0.32] or 3.06 mg/dl [0.36, 5.76]; P = 0.03) and improved the percent detection of low blood glucose levels (MD: 13.99% [6.06; 21.92]; P = <0.001) compared with the control condition. HbA1c did not change (MD: 0.01% [-0.18, 0.21] or 0.1 mmol/mol [-2, 2.3]; P = 0.88).

We concluded that current evidence suggests, on the basis of only three studies with a relatively small sample size and substantial methodological shortcomings, that psychoeducational interventions may reduce severe hypoglycaemic episodes and improve hypoglycaemia awareness, while maintaining HbA1c in adult persons with
type 1 diabetes on an intensive insulin schedule. The reported reduction in severe hypoglycaemic episodes of 1.03 episodes per 6 months would appear clinically meaningful, since severe hypoglycaemia leads to significant physical and psychological morbidity and societal costs.

We recommended more high-quality randomised controlled studies that look at the effects of psychoeducational interventions targeting hypoglycaemia on severe hypoglycaemia, hypoglycaemia awareness and fear of hypoglycaemia. In the current economic climate it is also important to look at the cost-effectiveness of these interventions to make recommendations for implementation in clinical practice.

Chapter 3 presents the process of development of HypoAware, targeting adults with insulin-treated type 1 and type 2 diabetes and problematic hypoglycaemia. HypoAware is developed with input from diabetes healthcare professionals and persons with diabetes and based on the evidence-based psychoeducational group intervention BGAT. Since uptake of BGAT in diabetes care is low, most likely due to its demanding nature, HypoAware combines the benefits of modern low-cost technology with the highly appreciated sharing of experiences and motivational aspects of a group intervention. HypoAware spans 4 weeks and consists of 3 face-to-face group sessions and 2 online modules.

The chapter also showed the feasibility, acceptability and preliminary results of HypoAware, which we studied with an uncontrolled multi-centre pilot-study in people with type 1 and type 2 diabetes and impaired hypoglycaemia awareness, frequent hypoglycaemic episodes and/or fear of hypoglycaemia. Feasibility and acceptability were assessed by means of self-report questionnaires on organisation, recruitment, delivery of HypoAware, retention and compliance, which yielded no major problems. Both trainers and participants were very satisfied with the program. The intervention materials required only minor changes. Pre-post intervention measurements in 37 participants from 8 hospitals showed non-significant trends towards a reduction of impaired hypoglycaemia awareness (from 81% to 68%) and a lowering of mild hypoglycaemic episodes per week (from 73% to 62%). Worries about hypoglycaemia, diabetes distress and confidence in self-care improved significantly (p<0.05).

These pre-post changes suggest the integrity of the original BGAT has not been compromised much by the shorter duration and online modules. In addition, the intervention had a minor drop-out (3 persons) which could be due to the attractiveness and ‘doability’ of the intervention.
We concluded that HypoAware is a feasible and acceptable intervention, suggesting improved opportunities of reach and intervention uptake in diabetes care. Future research should establish the effectiveness of HypoAware in a randomised controlled trial with a follow-up of at least 6 months to be able to include episodes of severe hypoglycaemia.

In Chapter 4, we described the design of the randomised controlled trial (RCT) of HypoAware and the design of the economic evaluation we performed alongside this trial.

In Chapter 5, we showed the results of this two-arms cluster-RCT, conducted in eight Dutch clinics in 137 adults with insulin-treated type 1 or type 2 diabetes and problematic hypoglycaemia comparing HypoAware with care as usual. Generalized Estimation Equation (GEE) analyses over 4 time points showed a non-significant 33% less episodes of severe hypoglycaemia in the HypoAware group as compared to the control group (RR=0.67; 95%CI: 0.39 - 1.16; p=0.150); a significant reduced odds of impaired awareness (OR=0.38; 95%CI: 0.15 - 0.95; p=0.038), a trend towards 20% less worries about hypoglycaemia (RR=0.80; 95%CI: 0.64 - 1.01; p=0.059) and a significant 30% less hypo-distress (RR=0.70; 95%CI: 0.56 - 0.88; p=0.002). There was no significant change in HbA1c within and between both groups. A post-hoc non-parametric t-test showed that over the 6 months study duration participants experienced 2.5 events of severe hypoglycaemia (IQR 1-10) in the control condition versus 1 event (IQR 0-6.5) in the HypoAware group (p=0.030).

We concluded that HypoAware resulted in improved self-management, which led to fewer severe hypoglycaemic episodes, improved hypoglycaemia awareness and less hypo-distress in comparison with usual care. We observed good program adherence, with 96% participating in ≥2 sessions (of 3) and 90% completing the two online sessions.

Although not all effects were statistically significant, we may assume clinical relevance, regarding the high impact of even minor reductions in severe hypoglycaemia. In our sample, the effects of HypoAware seemed more pronounced in persons without real-time continuous glucose monitoring (RT-CGM) use. Based on these results, HypoAware deserves further dissemination; however, more research is needed to examine the role of RT-CGM and the interaction with HypoAware in a larger sample of patients with problematic hypoglycaemia in different care settings.

In Chapter 6, we present the results of the economic evaluation of HypoAware versus care as usual from a societal and healthcare perspective. We used data from a 6 month, multi-centre, cluster-randomised controlled trial. We included 137 participants (see summary of chapter 5). Clinical outcomes were events of severe hypoglycaemia; proportion of persons with at least one event of severe hypoglycaemia; proportion of
persons with impaired hypoglycaemia awareness; quality adjusted life years (QALYs); and societal costs consisting of costs of healthcare consumption, informal care and lost productivity. The HypoAware group had one event of severe hypoglycaemia per person per 6 months fewer than the control group (95%CI: -5.0 to 3.0). The proportion of persons with at least one event of severe hypoglycaemia per 6 months was 22% lower (95%CI: -38% to -6%) and the proportion of persons with impaired hypoglycaemia awareness was 14% lower (95%CI: -31% to 4%) in the HypoAware group. The difference in QALYs was 0.0 (95%CI: -0.05 to 0.05). Mean total societal costs in the intervention group were €591 higher than in the usual care group (95%CI: -€974 to €2057). The mean incremental cost per event of severe hypoglycaemia prevented was €605. At a willingness-to-pay threshold of €20,000 per event prevented the probability that HypoAware was cost-effective in comparison with usual-care in the prevention of events of severe hypoglycaemia was 68% from a societal perspective and 69% from a healthcare perspective. For QALYs the ICER was 119,360 € per QALY gained with considerable uncertainty.

We concluded that HypoAware was not cost-effective from a societal perspective in comparison with usual care, but more promising from a healthcare perspective.

In Chapter 7, main findings of the studies described in this thesis are summarized and discussed, followed by methodological considerations and relevance for clinical practice and future research.