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Suboptimal behaviour and knowledge regarding overnight glycaemia in adults with Type 1 diabetes is common

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Introduction

Most adults with Type 1 diabetes (T1D) spend H3-hours a year with their diabetes care-team, therefore glucose self-management is essential. Hypoglycaemia is common, often feared, and limits achievement of near-normoglycaemia that decreases chronic complications[1-3]. An adult with T1D typically has two mild hypoglycaemia events weekly and one severe hypoglycaemia (SH) event, defined as that requiring assistance from another person for recovery, per year[4]. Over half of hypoglycaemia events occur overnight and are slept through[5, 6]. Nocturnal hypoglycaemia (NH) can be unrecognised as sleep reduces counter-regulatory responses[7], and NH can cause seizures, cardiac arrhythmias, and death[8]. NH risk can be reduced by flatter profile insulins[9], continuous glucose monitoring (CGM)[5], insulin pumps, particularly with a low glucose (insulin) suspend function[10], and patient education[11]. Identification of those who will benefit from education is key to enhance patient well-being and reduce carer and healthcare system burden. There are limited data regarding patient knowledge and behaviour related to NH prevention and care[12].

We developed a questionnaire for T1D adults to assess glucose self-management, particular that related to overnight BG. We believe this is the first such Australian study.

Subjects and Methods

The study was approved by Human Research Ethics Committees: Northern Sydney Local Health District, (#RESP/15/226) and St Vincent's Health (SVH), Melbourne, (#LRR137/15). Implied consent was obtained at Royal North Shore Hospital (RNSH) by survey completion and written informed consent at SVH.

Subjects were aged e 18 years with T1D or latent autoimmune diabetes of adults (LADA). All T1D or LADA adults attending RNSH or SVH diabetes outpatients during the 3-month study period were invited to participate (by CRL, RMcG or AJJ) whilst in the waiting room. After consenting they were provided with the paper questionnaire. Exclusion criteria were: age <18 years, pregnancy,

other diabetes types and inadequate English. Participants were asked to complete the survey whilst in-clinic. The 16-question survey (available free from the corresponding author) included: demographics, usual glycaemia-related behaviour, self-assessment of glucose management knowledge, response to six hypothetical pre-bed BG readings (4, 8, 11, 15, 18mmol/l (with moderately high (1.0mmol/L) blood ketones) and 20mmol/L) and desire for further diabetes education. Impaired hypoglycaemia awareness (IHA) status was based on self-report (full, partial or unaware) of hypoglycaemia awareness. Questionnaire completion time was recorded in a random subset. Recent (within 3-months) HbA1c results were retrieved from medical records. Responses to hypothetical BG-levels were categorised (by endocrinologists AJJ, GRF) as safe, unsafe or suboptimal. Suboptimal/unsafe responses included: not eating if pre-bed BG was d4mmol/L, not taking insulin and/or not rechecking BG overnight for pre-bed BGe 15mmol/L; and/or not testing ketones again for pre-bed BGe 18 mmol/L; eating without taking insulin for pre-bed BGe 11mmol/L and taking excess insulin to lower pre-bed BG levels. Excess insulin was defined as e 10% that calculated to correct the BG to 6mmol/L using the 'rule of 100' (100/total daily insulin dose, which estimates the BG lowering (in mmol/l) by 1 unit of insulin). The treating doctor was alerted if answers indicated potentially unsafe behaviours and (irrespective of answers), if participants desired education.

Data were managed in EXCEL (Microsoft, Redmond, Washington: Microsoft 2003), with random validation of 10% of data-entry and analysed in STATISTICA for Windows (StatSoft, Inc. (2012): STATISTICA (version 12, Oklahoma, USA) and ACCord (Analysis of Censored and Correlated Data, Boffin Software, version 2.0.10, Ryde, NSW). Normal distribution of continuous variables was assessed (Kolmogorov-Smirnov test) and descriptive statistics, Chi-square tests, t-tests or Welch t-tests and logistic regression were used. Significance was taken at $p<0.05$.

Results

Table 1 shows demographics of all 205 participants, and by Continuous Subcutaneous Insulin Infusion (CSII) and Multiple Daily Injections (MDI) use, by IHA status and by desire for further education. Over 90% of eligible patients participated; with 98% having T1D and 2% LADA. Seventy one percent attended RNSH (31% on CSII); 53% of SVH participants used CSII, (p=0.003). Apart from CSII use RNSH and SVH subjects and results did not differ significantly, hence data were grouped. The survey took 10-15 minutes, and 8% of surveys were incomplete, with missing responses averaging 6 % of questions.

Self-reported home BG monitoring habits are summarised in Table 2. The mean (SD) frequency of BG tests was 5.4 (2.7)/day, being higher in CSII vs. MDI users (p=0.01), but similar by IHA status or education desire. About one third of patients said that they never test their overnight BGs and 9% said they test every night. Self-reported BG testing frequency correlated inversely with concurrent HbA1c (r=-0.17; p=0.02) overall, in CSII-users (r=-0.29; p=0.01) and in subjects reporting full hypoglycaemia awareness (r=-0.20; p=0.02).

Thirty-one percent of participants reported not having in-date ketone test-strips at home, with no differences by insulin delivery mode, IHA status, nor education desire (all p>0.05).

In general, BG targets (Table 2) were similar in CSII and MDI users; except CSII-users targeted a lower bed-time BG (7.1 (1.2) vs 7.7 (1.4), p=0.005) and subjects desiring further education targeted a higher pre-breakfast BG, p=0.03. There were no significant differences by IHA status.

Self-reported severe hypoglycaemia (SH) frequency, (Table 2), was similar in all groups except for daytime SH being more common with CSII use and with IHA. The IHA group also had more frequent (>3/week) daytime hypoglycaemic episodes (experienced by 28% of those with IHA vs. 14% with intact hypoglycaemia awareness).

After waking with a NH, 71% of subjects reported they would test their BG pre-treatment. Only 44% reported testing soon after NH treatment, with most reporting not testing until morning. NH treatments are described in Figure 1. Patients were asked; "What determines when you test your blood glucose levels overnight?" The main reasons were if they "felt hypo" or were "awake for some other reason". Few would set an alarm to episodically test their overnight BG. Results were similar for CSII and MDI users and by IHA status ($p>0.05$).

After day-time extra exercise, alcohol or illness, 48%, 54% and 48% respectively reported they would not change their overnight BG care-plan. Only 30% said they would do so in all three situations (or two if they were a non-drinker, as were 15%). There were no differences by CSII vs. MDI use. Only 79% reported feeling confident dealing with these situations; 21% felt partly or not confident. Thirty-two percent of patients desired additional diabetes education, including 70% of those with less than full confidence and 22% of those confident in these situations. Further education was desired by 44% of subjects reporting IHA vs. 25% with full hypoglycaemia awareness, $p=0.006$. Education desire did not differ by insulin delivery modality nor by diabetes duration (both $p>0.05$).

Table 3 presents percentages of patients suggesting safe behaviour at each hypothetical pre-bed BG. Of all suboptimal/unsafe answers for the six BG levels, 20% were designated so because of risk for hyperglycaemia/ketosis, 15% because of hypoglycaemia risk, and 65% because of risk for both. Generally, safer responses were suggested by CSII-users, those who BG-tested more frequently and targeted higher bed-time BG levels. Results did not differ by IHA status, CGM use nor education desire. In univariate logistic regression analysis, only MDI use and fewer BG tests/day associated with higher rates of suboptimal overnight glucose control answers; OR (95% CI): 3.09 (1.64-5.81); $p=0.0004$ and 1.17 (1.04-1.32); $p=0.007$ respectively. Clinic site, gender, age, diabetes duration,

HbA1c, IHA status and SH frequency did not influence unsafe/suboptimal responses (p=0.73). In a multivariate logistic regression analysis adjusting for age, gender, diabetes duration, HbA1c and IHA status only MDI use and fewer BG tests/day remained independent predictors of suboptimal suggestions (OR (95% CI): 2.8 (1.4-5.4; p=0.003 and 1.17 (1.03-1.33); p=0.01).

Discussion

In this novel, clinically relevant study of T1D adults in two tertiary diabetes clinics, we demonstrated that it was feasible and time-efficient to use a self-administered survey to assess (self-reported) glucose care practices and identify patients with potentially risky behaviours related to overnight glucose management. Suboptimal practices, such as not having ketone test-strips, NH treatment and knowledge gaps were common.

It is recommended that adults with T1D test their BG levels ~~H~~4-times daily, including episodically overnight, and have in-date ketone test-strips for sick-day management and other circumstances of hyperglycaemia. The Australian government subsidises test-strips for BG, but not ketones. Less frequent BG-testing is usually needed during CGM-use, though this relatively costly, user-pay system was infrequently and usually episodically used by survey participants, and 'flash glucose monitoring' of interstitial fluid[13] was not available in Australia during this survey.

In our study the mean HbA1c was 7.8 (1.4)% (61.3 (15.8) mmol/mol, less than that of Australian adults with T1D in the 2011 ANDIAB report[14], (8.5 (1.8) %, approx. 69 (20) mmol/mol, n=993). We observed an inverse correlation between HbA1c and self-reported BG-testing frequency, as in other T1D studies[15, 16]. Whilst in our study the average number of reported BG tests per day, 5.4 (2.7), was good, approximately one third of patients reported never testing overnight. This confirmed our hypothesis of infrequent overnight BG-testing, despite our clinicians usually recommending episodic overnight testing given the frequency and risks of NH [4-6,8]. Nonetheless,

9% of patients reported testing every night, which may indicate fear of hypoglycaemia, or perhaps caution as they live alone (data not available).

BG levels targeted are in Table 2, but with a mean HbA1c of 7.8 % (61.3mmol/mol) the mean daily BG achieved would be ~9.8 mmol/l[17]. Subjects targeted higher BG levels at bedtime and overnight, sometimes in the teens, to avoid NH. CSII-users targeted lower pre-bed BG levels than MDI-users, (both >7.0 mmol/L), but similar levels at other times. Interestingly, adults with IHA did not target higher BG levels than those reporting normal hypoglycaemia awareness.

For hypoglycaemic conscious people the then recommended (oral) treatment was 15g refined carbohydrate to rapidly increase BG, followed by complex carbohydrate if the next meal was not within 20 minutes to prevent hypoglycaemia recurrence. Ideally, BG should be rechecked 15 minutes post-treatment and additional carbohydrate eaten if needed[18]. If consciousness is impaired glucagon injection or IV glucose administered by another person is required. Only 36% of survey patients described appropriate NH treatment, with 49% reporting they eat refined carbohydrate alone before returning to sleep, often without a BG test to confirm an adequate response. This could increase NH recurrence risk. Patients who consume complex carbohydrate alone may have a delayed return to normoglycaemia. We speculate this behaviour may indicate 1) need for education 2) lack of nearby optimal foods; 3) a desire to return to sleep promptly or 4) a desire to prevent post-NH hyperglycaemia through excess food. The impact of re-education on NH treatment is of interest.

A high percentage, (~50%) of survey participants reported that they would not change their overnight diabetes plan if they had extra exercise, alcohol or illness. This is surprising as these aspects are usually part of routine diabetes education, and are common scenarios, even though people with T1D often avoid exercise due to glycaemia related challenges[19]. Again, whilst we believe these practices may be widespread, we could not find another relevant publication. Not

modifying their glucose care-plan in these settings may increase patient risk of NH after exercise or alcohol, and of hyperglycaemia / ketoacidosis during illness. Whilst many patients desired additional diabetes education, one third of those who reported lack of confidence in adjusting their diabetes care-plan did not. Subjects reporting IHA had higher rates of (self-reported) SH, and were more likely to desire further education than those reporting normal hypoglycaemia awareness. Interestingly, education desire did not differ by diabetes duration nor insulin delivery modality, even though we speculated that CSII users may have had more recent education related to pump commencement or renewal. Our results suggest that it is difficult to predict who wants or needs additional education based on clinical factors alone, and the survey used herein may assist. The participating clinics provided additional education to subjects with unsafe behaviours reported in the survey or who requested education.

Very few patients always suggested safe responses to hypothetical bed-time BG levels. Mid-range levels, where no action was usually needed, had the highest rates of safe responses. Similar results were reported in a Type 2 diabetes (T2D) study of patients with risky glucose self-management behaviours[20]. Some studies demonstrate diabetes education benefit. Bhutani *et al.* found improved knowledge, attitude and practices and fewer symptomatic hypoglycaemia episodes in T2D patients after structured education with their doctor[21]. There is substantial evidence that education is key in improving diabetes management, especially in reducing hypoglycaemia[4, 22-25]. We found that CSII use was associated with higher rates of safer responses to hypothetical pre-bed BG levels. This may relate to more recent or additional education related to pump commencement or renewal, though their desire for further education was similar to that of MDI users. In addition, use of a bolus calculator (in insulin pumps) for insulin dose guidance was regarded as a safe choice in managing normal or high pre-bed BG levels. However, if the insulin sensitivity factor and insulin action duration are incorrect this may not be so, and also patients may not use the bolus calculator. Bolus advisors, such as in insulin pumps or “smart” BG meters, can improve insulin dose choices and

glycaemia[26, 27]. Lawton *et al.* showed that whilst most T1D patients perceive this technology as having advantages, it also has disadvantages such as dependence on the calculator, not remembering their insulin-carbohydrate and insulin sensitivity factor(s), and that these settings can change over time[28].

Study strengths are: novelty, clinical relevance, feasibility for clinical use, large sample size across two clinics and high participation rates, wide range of patient ages and diabetes duration, and analyses by insulin delivery mode, IHA status and desire for education.

Study limitations include an English-only questionnaire, risk of recall bias or reporting of ideal rather than actual behaviour and some missing data. In estimating the insulin dose to correct an elevated BG, a target (6mmol/L, which is a typical mean target across the day) was chosen for screening and the rule of 100 for each patient used to estimate their insulin sensitivity, which may not be accurate. NH treatment recommendations and safe behaviours may differ elsewhere, however responses in the independent clinics were similar. Only adults were studied, though with modification the survey may suit paediatric practices. BG meter downloads were not assessed to check reported testing frequency, though a practical challenge is the use of several meters. Meter records also reflect achieved BG levels, not those targeted, nor were formal questionnaires used to assess IHA, which would increase survey time and are usually a research tool. Hospital records for SH were not evaluated, as recall of SH in the prior year has been shown to be accurate and, based on our prior study, only a minority of T1D adults with a SH are transported to hospital[29].

In conclusion, our new self-administered survey is feasible for clinical use and reveals that many adults with T1D/LADA have suboptimal behaviours related to their overnight glucose control. Results also show substantial knowledge or implementation gaps and many desire additional diabetes education. Additional education may improve knowledge and implementation of relevant self-care. Such a survey may be incorporated into an annual review cycle, such as associated with diabetes complication screening, and may also be used pre- and post-diabetes education.

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Author Roles

CRL – Recruited patients, collected data, managed the database, performed descriptive statistical data analysis, interpreted the data and prepared the manuscript.

ASJ – Assisted with ethics approvals, assisted with data-base design and statistical analysis and contributed to the manuscript preparation.

RMcG – Assisted with patient recruitment, data collection and ethics approval.

JL – main Swedish tutor of CRL, was involved in design of the project, discussed results and revised manuscript.

ACK – Assisted with data interpretation and manuscript preparation.

RMacI- Assisting with data collection and manuscript preparation.

GW – Assistance with patient recruitment and manuscript preparation.

DNO –Assisted with data collection, interpretation and manuscript preparation.

GRF – Assisted with data collection and interpretation, and oversaw research carried out at RNSH.

AJJ – Designed the study, including questionnaire and database, obtained ethics approvals, recruited (SVH) participants, collected data, interpreted data and helped prepare the manuscript.

All authors contributed to the manuscript and approved the final version prior to submission.

Conflict of interest:

CRL – none

ASJ – none

RTMcG – none

JL – none

ACK – none

RJM – none

GMW – none

DNO – none

GRF – none

AJJ – none

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Figures and Table legends

Figure 1. Type of treatment for nocturnal hypoglycaemia.

Footnote: Abbreviations: carbohydrate – carb; Years – yrs.

Table 1. Subject demographics

Values are mean (SD) unless otherwise specified. P-values denote significance of comparisons between continuous variables (by t-tests) and of frequency counts (by Chi-square tests).

Abbreviations: continuous subcutaneous insulin infusion – CSII; hypoglycaemia – hypo; impaired hypoglycaemia awareness – IHA; multiple daily injections – MDI; years - yrs

Table 2. Glucose testing habits, targets and hypoglycaemia frequency

Values are mean (SD) or %, unless otherwise specified. The table shows self-reported BG levels targeted (not achieved) at various times of the day, the frequency of BG testing at various times of the day, and hypoglycaemia frequency during the day and overnight, including SH in the last year. Values are shown for all subjects, and stratified by insulin delivery mode, IHA status and further education desire. P-values denote significance of comparisons between continuous variables (t-tests) and of frequency counts (Chi-square tests).

Abbreviations: blood glucose – BG; continuous subcutaneous insulin infusion – CSII; education – educ'n; hypoglycaemia – hypo; impaired hypoglycaemia awareness – IHA; multiple daily injections – MDI

Table 3. Percentage of safe hypothetical pre-bed BG treatment answers

The table outlines the percentage of safe answers given by all participants, and as divided by insulin delivery mode, IHA status, and by desire for further diabetes education. As indicated with an asterisk *, there were significant differences: between CSII and MDI users for scenarios with BG 8, 18 (with moderate ketones) and 20 mmol/l; by IHA status in the BG 8 mmol/l scenario. Overall

CSII-users suggested safer responses more often than MDI-users, p=0.0003. There was no difference between subjects with regard to education desire.

Abbreviations: continuous subcutaneous insulin infusion – CSII; hypoglycaemia – hypo; impaired hypoglycaemia awareness – IHA; multiple daily injections – MDI

Figure 1.

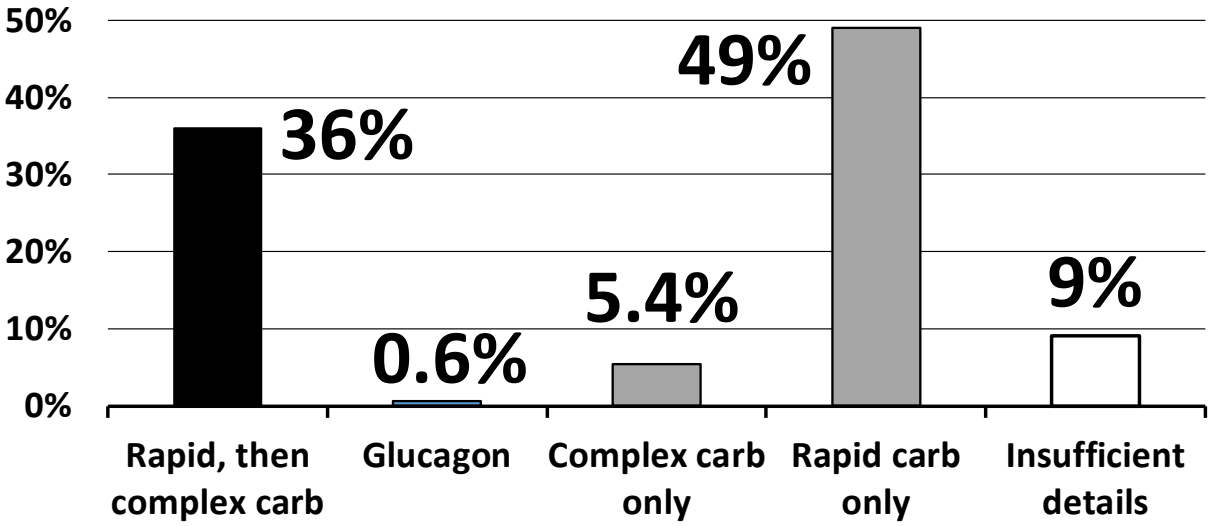

Table 1

	Total	CSII	MDI	p	Hypo aware	IHA	p	Desires more diabetes education		
								Yes	No	p
n	205	77	128	-	131	74	-	65	140	
Age (yrs)	41 (17)	41 (17)	41(17)	0.96	37 (16)	47 (17)	**0.0001**	44 (17)	39 (17)	0.08
Gender (%male)	50	34	59	**0.0004**	48	53	0.53	48	50	0.72
Yrs T1D	20 (16)	20 (14)	20 (17)	0.81	17 (13)	27 (18)	**<0.0001**	21 (17)	20 (15)	0.64
HbA1c (%)	7.8 (1.4)	7.8 (1.1)	7.7 (1.6)	0.50	7.7 (1.3)	7.8 (1.7)	0.83	8.0 (1.9)	7.6 (1.2)	0.17
HbA1c (mmol/mol)	62 (8)	62 (12)	61 (18)	0.50	61 (14)	62 (19)	0.83	64 (21)	60 (13)	0.17
% on CSII	38	100	0	-	36	23	0.51	35	38	0.71

Table 2.

	Total	CSII	MDI	p	Hypo aware	IHA	p	Educ'n Yes	Educ'n No	p
(Self-reported) Blood glucose target										
Pre-breakfast	6.5 (1.2)	6.5 (1.0)	6.5 (1.3)	0.86	6.5 (1.2)	6.6 (1.2)	0.61	6.7 (1.1)	6.4 (1.2)	0.09
Pre-lunch	7.0 (1.3)	6.9 (1.3)	7.0 (1.3)	0.46	7.0 (1.2)	6.9 (1.4)	0.59	7.0 (1.3)	6.9 (1.3)	0.63
After Lunch	6.9 (1.3)	6.7 (1.2)	7.0 (1.3)	0.11	7.0 (1.3)	6.7 (1.2)	0.07	7.0 (1.2)	6.8 (1.3)	0.36
Pre-dinner	7.1 (1.3)	6.9 (1.1)	7.2 (1.4)	0.06	7.1 (1.2)	7.0 (1.5)	0.55	7.2 (1.4)	7.0 (1.3)	0.47
Overall Daytime	6.9 (1.0)	6.7 (1.0)	6.9 (1.0)	0.16	6.9 (1.0)	6.8 (1.1)	0.46	7.0 (0.9)	6.8 (1.1)	0.20
Pre-bedtime	7.5 (1.4)	7.1 (1.2)	7.7 (1.4)	**0.004**	7.6 (1.4)	7.3 (1.3)	0.23	7.7 (1.1)	7.4 (1.5)	0.17
Overnight	7.1 (1.3)	7.0 (1.1)	7.2 (1.4)	0.17	7.2 (1.4)	7.0 (1.3)	0.47	7.3 (1.0)	7.0 (1.4)	0.12
(Self-reported) Blood glucose testing frequency										
BG tests / day Mean (SD)	5.4 (2.7)	6.0 (2.9)	5.1 (2.4)	**0.02**	5.3 (2.6)	5.7 (2.8)	0.26	5.9 (3.0)	5.3 (2.5)	0.17
Overnight BG testing (%) (never / sometimes / every night)	27 / 64/ 9	19 / 68 / 13	32 / 62 / 6	0.07	29 / 60 / 11	25 / 70 / 5	0.30	24 / 65 / 11	29 / 63 / 8	0.63
(Self-reported) Hypoglycaemia frequency										
Day time hypos / week (%) (< 1 / 1-3 / > 3 times)	41 / 40 / 19	29 / 45 / 26	48 / 37 / 15	**0.02**	43 / 43 / 14	36 / 35 / 28	**0.04**	38 / 35 / 26	42 / 42 / 16	0.21
Overnight hypos / month (%) (never / 1-4 / > 4 times)	21 / 65 / 13	16 / 66 / 18	25 / 65 / 10	0.13	18 / 67 / 15	27 / 62 / 11	0.35	16 / 68 / 16	24 / 64 / 12	0.45
SH (%) (in last yr)	21	23	20	0.51	12	36	**<0.0001**	25	19	0.33

Table 3.

	Hypothetical Pre-Bed BG ± ketones scenario						
mmol/L	**4**	**8**	**11**	**15**	**18 + 1.0 ketones**	**20**	***Overall***
Safe (%) - All	54	87	95	47	70	63	28
Safe (%) - CSII users	62	**94***	97	53	**79***	**73***	**43***
Safe (%) - MDI users	48	**83***	94	43	**64***	**57***	**20***
Safe (%) - Hypo aware	54	**82***	96	47	72	62	27
Safe (%) - IAH	53	**95***	93	47	66	64	30
Safe (%) – Desires education	60	91	94	47	68	62	32
Safe (%) - No desire for education	51	85	96	47	72	64	27

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