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Mobile health for drug dose optimisation

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Abstract—**Mobile health monitoring in the management of long term conditions has potential benefits for patient care, especially when coupled with active adjustment of medication dosage. We report studies of patient-led self-titration of oral glucose lowering medication (OGLM) and insulin in type 2 diabetes, and dose adjustments (including dose increases) in oral chemotherapy for metastatic colorectal or breast cancer. Monitoring compliance was high in each case, and the feasibility of patients self-titrating OGLM or insulin following an agreed treatment plan was demonstrated. Chemotherapy dose increases supported by detailed toxicity profiles collected by phone have also been demonstrated.**

I. Introduction

THE use of telemedicine for monitoring patients with chronic diseases or long term conditions has been explored for a number of years, and the rise in ownership of mobile phones in the developed and developing world has led to a focus on mobile health [1]. Often these systems will facilitate remote monitoring of patients, with the increased availability of patient data leading to improved clinical management and patient health outcomes. Limitations of open-loop monitoring have been demonstrated in a number of studies, for example [2], therefore closed-loop monitoring with directly-targeted dose adjustments for the management of long term conditions is of particular interest.

We report three studies focussing on dose optimisation in a variety of treatment regimens. The first study examines titration of insulin injections in type 2 diabetes, where the risk of side-effects is significant. The lessons learnt in the first study have led to a second study with the aim of optimising the dose of oral glucose lowering medication (OGLM), also in type 2 diabetes. The final study involves the optimisation of an oral chemotherapy drug in the treatment of metastatic colorectal or breast cancer, where there is a high risk of potentially life-threatening side-effects.

Each study used an individually-customised version of a mobile health platform developed by OBS Medical (Abingdon, UK) based on earlier research [3]. An overview of the platform is provided in Fig. 1, showing a mobile phone application for collection of the relevant electronic patient diary information and real-time secure transmission to the study server. The server stores the data for access by the study clinicians via a secure website, and also provides automatic analysis and monitoring of the incoming data to allow summaries and alerts to be produced as appropriate. The implementation details for each study are described in the sections below.

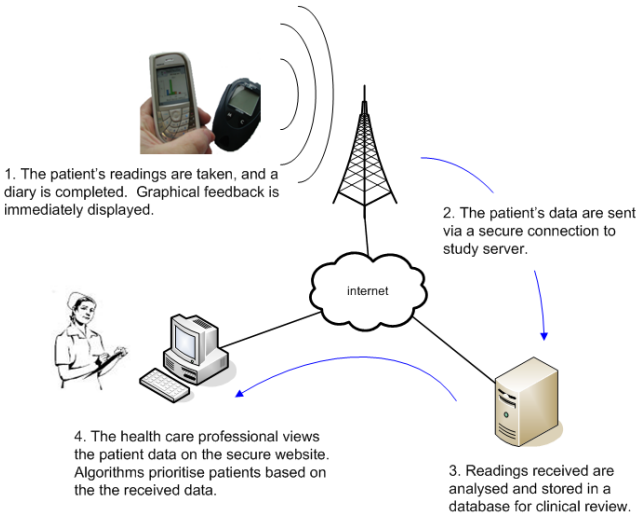

Fig. 1: Mobile health architecture

II. Insulin Treatment for Type 2 Diabetes

When maximum doses of OGLM are insufficient to maintain blood glucose control in type 2 diabetes, patients may be converted to insulin treatment. This can be a challenge for patients for many reasons, including a fear of needles, a perceived failure in their management, or anxiety about the complexity of the treatment [4]. In addition, there is a risk of hypoglycaemia when a patient injects insulin, a risk not present in most oral medication treatments: if the insulin causes the patient's blood glucose level to drop too far, the patient can become confused, disorientated or lose consciousness. It is therefore necessary to titrate gradually to a dose which is high enough to restore glycaemic control, but not too high as to cause hypoglycaemia. Patients may find this process difficult and it may be very time-consuming for general practice to fully support these patients. We therefore conducted a study of patient-led self-titration of insulin dosage, supported by a telehealth nurse.

A. Study Design

Patients recently converted to insulin treatment, or about to commence insulin treatment, were considered for this study if they continued to have poor glycaemic control. Each patient was given a mobile phone with a pre-configured application and a Bluetooth-enabled blood glucose meter to transmit the readings to the phone. The

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patients were asked to measure their blood glucose before breakfast each day (this fasting state provides a good indication of overall glycaemic control) with the measurements from the blood glucose meter being transmitted in real-time by Bluetooth to the mobile phone application. Patients were also asked to estimate the number of hours since their last meal (as an indicator of fasting/post-prandial status) and the level of exercise carried out that day (which may affect blood glucose levels and insulin effectiveness). They were then shown on the mobile phone screen a colour plot of their readings to guide the insulin dose adjustment (see Fig. 2). Patients were provided with instructions suggesting that they should consider increasing their dose by 2 units every three days, if two of the three previous days' fasting readings exceeded 6.7mmol/L, provided that no reading was below 4.0mmol/L. The telehealth nurse would review the data on the web page every 2 – 3 days and initiate contact with the patient if: (i) no readings were received for three or more days; (ii) seven or more days had fasting readings above 7.5mmol/L; (iii) any single reading was below 4.0mmol/L; or (iv) if there were any other situations of concern, at the discretion of the nurse. The telehealth nurse also provided general advice and motivation.

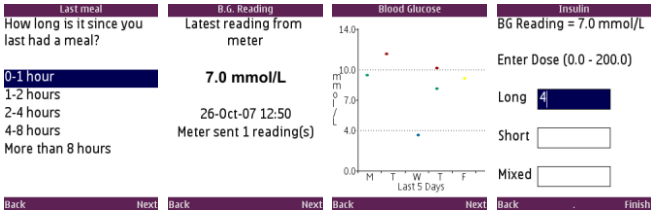

Fig.2: Phone screens from the insulin titration application

B.Results

Full results have been reported previously [5] for 23 patients who used the system as detailed in Table 1. Blood glucose monitoring compliance was generally high, although there was high inter-patient variability in the fasting reading compliance

The use of the mobile-phone application supported the optimisation of insulin dosage and was associated with improved glycaemic control with respect to the start of the study. Patient-led titration was evident, although the strategies to achieve this were occasionally outside the titration protocol; adjustments were often made by patients without the study protocol requirement for three fasting blood glucose readings from three consecutive days being met. The mean change in insulin dose was 17 (SD 26) units after the six-month study. This relatively large variance is indicative that even though insulin dose changes occurred, there was some reluctance from patients to increase their dose.

III.ORAL MEDICATION FOR TYPE 2 DIABETES

The demonstration that mobile phone technology is appropriate for titration of insulin in type 2 diabetes led us to design a study of self-titration of oral medication. This allows the optimisation of the dose without repeated visits by the patient to their general practice. The first treatment step for a newly diagnosed patient with type 2 diabetes is lifestyle modifications, such as diet and exercise. This will usually be insufficient to either restore or maintain glycaemic control, and subsequently OGLM will be prescribed. In the UK, the first drug to be prescribed is usually metformin, which can cause gastrointestinal side-effects. Therefore the patient is initiated on a low dose and the dose is gradually increased until glycaemic control is restored. If this cannot be achieved at the maximum dose, or the maximum tolerated dose, then a second agent is added and titrated. Dose adjustments generally require the patient to attend their general practice, and we therefore conducted a study to investigate the feasibility of patients self-titrating their medication, following an agreed treatment plan.

TABLE I
MOBILE HEALTH SYSTEM USAGE

Treatment	Insulin	OGLM	Capecitabine
Patients (n)	23	7	26
Duration of monitoring (days) [a]	189 (162 – 376)	102 (94 – 243)	119 (7 – 213)
Blood glucose readings per week [b]	6.2 (3.0 – 7.0)	5.2 (3.9 – 6.6)	n/a
Fasting readings per week [b]	2.1 (0.0 – 6.1)	2.4 (1.7 – 3.1)	n/a
Side-effect diaries per week [b]	n/a	n/a	12.8 (10.3 – 14.0)

[a] Values are mean (range); [b] Values are median (range)

A.Study Design

Patients with type 2 diabetes treated only with OGLM at sub-maximal doses and with poor glycaemic control have been recruited from general practices in the Thames Valley, UK. Each patient and their general practitioner agreed an individual treatment plan detailing the patient's baseline medication and each increment in dose and medication type up to a maximum dosage. As in the insulin titration study, patients were given a mobile phone and Bluetooth-enabled blood glucose meter. Patients are asked to measure their blood glucose six times a week, including three fasting measurements. Once the blood glucose readings have been sent to the phone, the patient is asked to identify the fasting readings. The patient continues to monitor their blood glucose for 21 days and is then asked to review their fasting readings to decide if a dose increase is appropriate. When considering whether to increase the dose, patients are advised to ensure that they have recorded six fasting readings in the previous two weeks, and that at least half of these are above 6.1mmol/L, in the absence of any reading below 4.0mmol/L. Once the patient has acknowledged that the conditions for advancing to the next treatment step have been met, he or she is asked to confirm when they are starting to take the new dose (as the new medication may not be immediately available, for example) and the 21-day cycle then repeats.

The website prioritises patients depending on their state

within the titration cycle, allowing for periodic review by a telehealth nurse. The nurse can communicate with the patient using SMS text messages sent through the website, and is provided with a template of standard messages for motivation, support, and feedback on patients' progress. Free-text messages can also be sent.

B.Results

To date, seven patients have been recruited to use the mobile phone for self-titration of OGLM, as detailed in Table 1. These preliminary results show a good degree of compliance with the blood glucose monitoring schedule, and a relatively consistent fasting reading compliance.

Of the seven patients, five have successfully self-titrated their medication; one patient has had their medication reduced following clinical review; and one patient has not yet adjusted their medication due to a reluctance to add a second drug to their treatment.

These early results indicate that it is feasible for patients to self-titrate their OGLM following a pre-agreed schedule. Full results will follow for a larger group of patients, randomised between this intervention and usual care, and report a comparison in glycaemic control between the two arms of the study.

IV.ORAL CHEMOTHERAPY FOR COLORECTAL OR BREAST CANCER

Capecitabine is an oral chemotherapy drug used in the treatment of advanced metastatic colorectal or breast cancer. The standard dosing regimen for capecitabine is based on three-week cycles, during which the patient takes tablets twice daily for two weeks, followed by a week without treatment. Up to eight cycles are prescribed, during which period the dose of capecitabine can be reduced or suspended due to the onset of cytotoxic side-effects such as neutropenia, diarrhoea or vomiting. The standard dosing regimen is derived from early trials in which one third of patients had developed side-effects requiring dose reductions [6]. There may however be many patients who could tolerate a higher dose of capecitabine, with the possibility of increasing the survival time of those patients. We conducted a study to investigate the feasibility of capecitabine dose increases supported by patient toxicity profiles collected in real-time using a mobile phone application for self-recording of symptoms during treatment.

A.Study Design

We previously reported the results of a feasibility study carried out with a mobile phone application for patients with colorectal cancer receiving capecitabine in the adjuvant setting [7]. This system collected twice-daily diaries from patients with details of the most common capecitabine-related side-effects (diarrhoea, vomiting, nausea, mucositis and hand-foot syndrome) as well as temperature, as a marker of possible infection – see Fig. 3. In the new study, the diary was extended to include peripheral neuropathy (a common side-effect of oxaliplatin, which is often used in combination with capecitabine for colorectal cancer), and dosage information, with patients reporting their medication intake. A set of alert criteria, simplified from the previous study, was implemented with alerts classified as either amber or red depending on their severity. The phone was programmed with self-care advice which was displayed on the screen whenever the relevant alert condition occurred (for example, to take loperamide for moderate or severe diarrhoea). Amber alerts were batched and sent to the study nurse at pre-defined times of the day, although red alerts were immediately paged to the nurse as these were of sufficient severity to warrant immediate attention and the nurse was mandated to contact the patient within 30 minutes of the alert being generated.

Dosing tables were developed allowing for three capecitabine dose reductions of 15%, down to 85%, 70% and 55% of the patient's starting dose. Dose reductions were made within a treatment cycle as a result of severe side-effects or prolonged moderate side-effects. If the drug could still not be tolerated at the 55% level treatment was stopped. Dose increments of 10% were also defined, allowing doses of 110%, 120% and 130% of the standard starting dose, but these were only implemented following a full assessment, including blood tests, during the patient's regular clinic visit at the end of each three-week cycle. They also required the patient to have had negligible side-effects during the cycle which had just been completed.

Criteria for dose adaptation were developed but, in contrast to the diabetes studies detailed above, these were clinician-led rather than patient-led, as patient-led medication titration is not appropriate in the oncology setting.

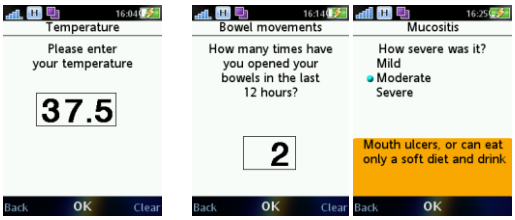

Fig. 3: Phone screens for chemotherapy side-effect monitoring

B.Results

26 patients commencing capecitabine treatment were recruited from the Churchill Hospital, Oxford, UK. All patients used the system for the duration of their capecitabine treatment, as detailed in Table 1. The figure for diary completion compliance excludes periods where patients were hospitalised and treated as in-patients during the study.

Of the 26 patients, three did not receive a second cycle of capecitabine and were therefore not eligible for dose adjustments; seven remained on the starting dose; eight patients received at least one dose reduction from the starting dose; and eight patients had at least one dose increase. Of the eight dose increases, three were subsequently dose-reduced again. These results from our

preliminary analysis demonstrate that dose increases are feasible in capecitabine treatment when supported by close toxicity monitoring, thereby making it possible to individualise a patient's dosage.

V. Discussion

Three mobile health studies have been reported, in the diabetes and oncology settings, with different degrees of risk requiring different degrees of monitoring and clinical oversight. OGLM for type 2 diabetes may be considered the safest, due to the nature of the side-effects, and therefore monitoring of fasting blood glucose levels less frequently than once per day is appropriate. Following clinical review, feedback is sent to the patient by text message, which does not require their immediate attention. Insulin injections, however, are associated with a risk of hypoglycaemia, and more frequent daily monitoring of fasting blood glucose is therefore desirable, especially with the much shorter titration cycle (three days, compared to 21 days for OGLM). Finally, for oral chemotherapy, twice-daily monitoring and self-reporting of symptoms provide a highly detailed toxicity profile which can guide and track the effect of increased doses. Frequent monitoring is required here to quickly detect the onset of side-effects associated with toxicity.

Across the three studies, monitoring compliance was high, even among the least compliant patients. The identification of fasting readings in the insulin study was lower than expected, an issue compounded by having to infer the fasting state from a non-explicit question and the inability to retrospectively tag previous readings. This demonstrates the need for a flexible system which can cope with varying use cases by different patients. The twice-daily monitoring in the chemotherapy study was particularly demanding, but still appeared to be well accepted. This may be due to the use of the mobile phone becoming integrated with the routine of taking the tablets, or a perceived value associated with the assurance of knowing that the symptom data transmitted by the phone was regularly monitored by study nurses.

Clinical monitoring was maintained in each study, with data review and automatic generation of summaries and alerts tailored as appropriate to the needs of each study and to the risk of side-effects from the relevant drugs. Communication with patients varied with the degree of urgency in the studies, ranging from text messages for patients to review at their leisure, to mandated phone calls within 30 minutes.

Each study has also demonstrated dose adjustments as steps in the individual optimisation of patients' medication dosage. In each case, titration was based on review of previously-collected data, with subsequent monitoring to assess the effect and suitability of further adjustments. Preliminary results from the type 2 diabetes OGLM study indicate that five of the seven patients have successfully adjusted their medication, one patient has had their medication reduced, and one patient has been reluctant to adjust their treatment. Patients in the insulin titration study increased their dose by a mean of 17 units over six months, but may have been reluctant to make further adjustments. This may have been due to lack of familiarity with patient-led titration, the need for reassurance from the patient's clinician or the telehealth nurse, or anxiety relating to hypoglycaemia. Such barriers suggest that self-titration using the phone application alone is not a complete solution, and that on-going provision of advice, support and motivation is a key component. For mobile health monitoring to be efficient in the diabetes and oncology settings, a telehealth nurse is needed to support patients, although the number of patients which each nurse can support is likely to be sufficiently large for mobile health still to offer substantial efficiency savings.

Prioritisation of patients and graded alerts are important in helping telehealth nurses to manage large groups of patients. Such a strategy was employed in the chemotherapy study where immediate response to severe toxic side-effects was required. In this setting, the nature of the telehealth nurse support was different from the diabetes studies, being predominantly reactive to deterioration in the patient's condition rather than being focused on supporting patients with the self-titration of their medication.

The small sample sizes are a limitation of each of the three studies, as is the lack of randomisation between the mobile phone intervention and usual care in the insulin and chemotherapy studies. Further large randomised clinical trials would be required to fully assess the changes in patient outcomes.

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