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Patient compliance: when was the last time you took your medication?

Objective therapy Compliance Measurement (OtCM) will allow healthcare professionals to monitor patients' medication compliance, reducing the risk of adverse reactions to medication and patient fatalities

Patient compliance is crucial for the maximum efficacy of any medical therapy. However, medication compliance remains a serious issue within certain patient groups, in particular those with complex dosing regimens and those with medications that have unusual instructions for usage or administration. Prescribing for older patients is particularly challenging as they may be more likely to have chronic medical conditions that require multiple drug therapies. Noncompliance, either through incorrect dosage or incorrect timing of administration, may lead to an increased chance of adverse reactions and even patient fatalities. In the Netherlands alone, the cost of poor medication compliance has been estimated at €4.3billion annually (based on 2004 figures). Taken at the European level, it causes the death of 150,000 people annually, and the money wasted amounts to over €100 billion. Consultation, education and behavioural modification have only limited success in increasing compliance; 40–70% of patients suffer from "therapy failure" or develop a new medical problem due to incorrect use of medication.

The Compliers Group, Eindhoven, Netherlands, has developed an Objective therapy Compliance Measurement (OtCM) system that allows healthcare professionals to remotely monitor patients' medication compliance and correlate therapy outcomes.

The OtCM solution is based on a number of novel technologies designed to replace the standard film or foil currently used in existing standard blister packaging. By using a so-called system-on-foil technology, a polymer-based electronic circuit is printed directly on a self-adhesive blister label that fits any existing (standard) blister package. Comprising a number of conductive tracks running under each blister, the system-on-foil technology allows silicon, or a printed polymer integrated circuit, to record the event when a track is broken by the removal of the tablet. This includes time of the event, position of the tablet removed from the blister and any other clinically relevant data. The electronic circuit also contains radio-frequency identification (RFID) technology to enable the information stored to be retrieved using an RFID reader. Furthermore, the integrated circuit may be programmed using the RFID interface (during the blister-filling phase) with information about the filling medication, logistical data and even unique codes to prevent counterfeiting.

The advantage of a system that allows monitoring of patients' adherence to medication dosing is clear: pharmacists and other healthcare professionals will have access to objective and specific details of medication therapy, measured accurately; and, in the event of unacceptable deviation, timely warnings can be given so that intervention is possible. This information alone is potentially enough to prevent costly changes to treatment regimens (based on misinformation from the patient) and may help to prevent the many thousands of adverse drug errors that occur throughout Europe each year. For patients, OtCM systems allow improved effectiveness of medicines, increased user confidence and avoidance of unnecessary changes to original medicines. ■

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OtCM (Objective therapy Compliance Measurement): smart blister packages for measuring patient compliance

Smart blisters are a new approach in the electronic monitoring of patient compliance with oral medication. An innovative OtCM system has been developed and tests have proved its validity

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Patient compliance or adherence – defined as "the extent to which a person's behaviour coincides with the medical or health advice"[1] – is a basic prerequisite for effective and successful treatment of diseases. Medication compliance is an essential part of the patient's overall compliance. Poor medication compliance may cause poor therapy outcomes and increased healthcare costs.[2] In addition, noncompliance is one of the most important elements responsible for differences between effectiveness and efficacy of certain drugs.[3]

As the WHO estimates that only 50% of patients suffering from chronic diseases in industrial nations and even fewer than 50% in developing countries are compliant with their therapy, the need for compliance-improving measures to enhance patients' safety, and most probably to save costs, becomes obvious. It is even stated that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments".[2]

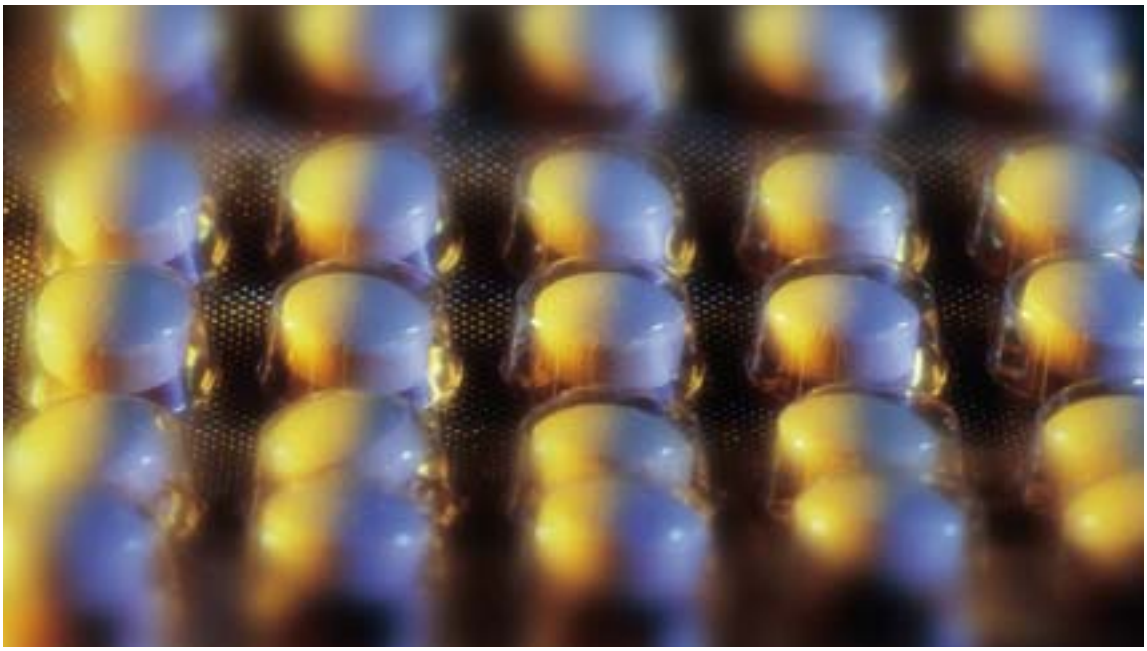
However, an accurate assessment of patients' compliance behaviour is necessary to achieve effective and efficient treatment planning.[2] Analysis of patients' medication intake behaviour is considered to be a vantage point for the development of suitable strategies to improve patients' compliance. Information about patients' compliance is also necessary to interpret results of clinical trials realistically,[4] to assess dose–response relationships of a drug, to allow valid analysis of treatment efficacy,[5] and to distinguish between noncompliers and non-responders.[6] The significance of patients' medication compliance and increasing research in this field over the last few decades has resulted in the establishment of a new branch of research called pharmionics. Pharmionics is the discipline concerned with quantitative analysis of what patients do with prescription drugs.[7]

Lack of an ideal method for compliance measurement

To date there is no method that fulfils all requirements for valid compliance measurement, although reliability and validity of the testing method is crucial to get useful data.[5] Existing methods can be classified as direct and indirect methods. Direct methods include direct observation of the patient administering the medication and quantitative analysis of the drug in a biologic fluid collected from the patient. Rather than the drug in the form of its parent compound, its metabolites or even a biological marker added to the drug formulation can also be analysed. Analysis of blood samples taken is also used for therapeutic drug monitoring (TDM). Unfortunately, TDM is only representative for a limited period of time before blood sampling and the utility is reduced by pharmacokinetic variability of patients. Direct methods provide reliable evidence that the patient has used the medication.[5] However, they are very laborious, cost-intensive and often not practicable.

Indirect methods are easier to adopt, but the resulting data are less objective and often overestimate compliance. Indirect methods comprise patient self-reports, questionnaires, pill counts, prescription refills, patient diaries, assessment of patients' clinical response and electronic medication monitors.[8] The latter have replaced pill counts as reference standard.[5] In contrast to pill counts, electronic monitors allow a continuous assessment of drug dosing over time and show when omissions occur. Electronic monitoring is done by integrating a small time-keeping microcircuit into drug packages in such a way that the time and date are recorded whenever a dose of drug is removed from the package.

Until now the well-established MEMS® system (Medication Event Monitoring System; Aardex Ltd), which works with conventional medicine bottles equipped with a clock, microswitch and memory in the caps, has been considered to be the "gold standard" for measuring the patient's actual dosing history. The latest approach in the electronic monitoring of patient compliance with oral medication, however, is to use electronic or "smart" blisters. Some examples of smart blisters currently used in practice are IDAS (Intelligent Drug Administration System; Bang & Olufson Medicom), Med-ic ECM (Electronic Compliance Monitor; IMC); Cypak/Cerepak (MeadWestvaco Healthcare)[9,10] and Stora Enso Pharma DDSi (www.storaenso.com/pharma). In each of these systems the blister package containing the oral medication is



embedded in an additional, specially designed wallet. In contrast, the OtCM system (Objective therapy Compliance Measurement), developed by The Compliers Group (TCG) in the Netherlands, can be attached directly to an existing, commercially available standard blister package without altering the medication blister package and without affecting the stability of the medication. There is no need for a dedicated design, which makes the system very flexible and promising for broad application. An additional major advantage of smart blisters over the MEMS system is the 1 : 1 ratio of documented events. Every tablet removal causes an extra event, whereas during one opening of the MEMS cap several doses could be removed.

Components and functionality of the OtCM-system

The OtCM system consists of hardware and software products:

- Electronic blister packages that record and store the time and date of every medication removal.
- A radio-frequency identification (RFID) reader (DataTaker®) that reads out the data and transfers them wirelessly to a secure website.
- Software to analyse the recorded data.

The add-on version of OtCM-activated blister packages is produced by attaching self-adhesive RFID labels to standard blister packages. The labels consist of a foil on which lines of conductive ink are printed, an antenna, a battery and an active RFID chip. The innovative assembly and production is done in cooperation with the Schreiner Group in Munich, Germany.

RFID technology already used in the healthcare system is mostly based on passive RFID tags, for example for tracking and tracing medical products. TCG's RFID technology represents active RFID tags with a memory for various information (production process information, temperature, therapy compliance information) and is applicable at "item level", versus the normally adopted "package level". The 13.56 MHz RFID OtCM standard meets the healthcare safety requirements and supports the near-field communication (NFC) platform of several manufacturers of mobile phones.

At regular time intervals this RFID chip sends an electric current through the conductive lines crossing each cavity of the smart blister package. The removal of medication causes rupture of the conductive line, and this is registered and stored in the RFID chip as an event, together with the time, date and location of the removed oral drug formulation in the blister package.

A device called DataTaker is used to programme and read wirelessly the RFID-enabled medication blister packages (RFID NFC). The device is a mobile telephone-related product using existing, standard, globally available wireless GSM/GPRS data net-works. By putting the smart blisters on the DataTaker workstation, the recorded information is sent to the OtCM URL-accessible database server and stored in a dedicated software program, where it is accessible for authorised practitioners.

Automated transactions process the data, and the results are displayed in different forms, for example in a graphical form. Via a query manager, therapy compliance events can be exported to other software programs and analysed in more detail.

OtCM validation studies

A prerequisite for a broader application of the OtCM system is to investigate the validity of the OtCM smart blisters for measuring patients' compliance. Therefore, functionality and reliability of the system were tested in an experimental setting.

Ninety-four OtCM-enabled blister packages, each containing 10 placebo capsules and one DataTaker, were used for a first validation study. The blisters were "handed out" to fictitious patients. To "hand out" means to allocate one specific blister to a specific patient by putting the blister on the DataTaker and "writing" the patient's name or number on the RFID chip. The capsules were then pressed out of the blister cavities following a predefined sequence. In order to show robustness, some of the blister packages were exposed to different physical conditions. The removal time was taken by a radio-controlled clock, and the date and the location of the capsule on the blister package were immediately documented on a paper worksheet. When all the capsules had been removed, the empty blister packages were "handed in": that means that the stored data were read out by the DataTaker and transmitted to the internet-accessible OtCM database server. The online retrieved data were compared with the data in the written documentation, and the smart blister packages were evaluated according to the following criteria:

Functionality

The functionality of the blisters was determined by calculating the percentage rate of blisters that were readable after removal of the capsules. Blister packages that were not functioning from the beginning (at "hand out"), were excluded from the study.

Accuracy

Accuracy referred to the percentage rate of correctly calendared removals. As described above, the time and date of each capsule removal was measured and compared to the date and time registered by the OtCM system. Differences greater than 10 minutes were assigned as errors.

Sensitivity

Sensitivity is the ability of the system to register each event and was calculated as the number of registered removals divided by the number of actual removals.

Specificity

Specificity implied that only actual removals were recorded. To measure specificity from 12 blisters tested under normal laboratory conditions, fewer than 10 capsules were removed. The number of nonregistered events (10 minus the number of registered events) was compared with the number of capsules remaining in the blister packages. Specificity was calculated as the number of nonregistered removals divided by the number of capsules remaining in the blisters.

Robustness

Robustness was evaluated by measuring functionality, accuracy and sensitivity after applying various physical conditions and by comparison of the results with the results achieved under normal laboratory conditions. Conditions were chosen with regard to conditions in practice – that is, the conditions that would most probably occur in daily routine:

- Temperature: five OtCM blisters were stored during the tests at 2–8 °C and 40 °C, respectively.
- Agitation: five blisters were tested after dropping them from 1.2 m.
- Field conditions: 15 blisters were used at home by five different employees of the pharmacy department, simulating routine intake of medication.

Validity of the OtCM system

The results of our studies document the functionality and reliability of the add-on version of OtCM-activated blister packages.[11,12] Detailed results of the tests run under normal laboratory conditions and various "robustness" conditions with the first batch of OtCM blister packages are shown in Table 1. Of the 94 OtCM blister packages tested, 82 were functioning (87.2%) and further evaluated. These blister packages showed a total accuracy rate of 95.7%, which is highly acceptable since they were prepared manually. Due to a programming error in the calendar clock, the times recorded during the tests had to be adjusted according to a defined algorithm. The data presented here refer to the adjusted results. This programming error has already been eliminated and will not affect the use in the future, as results of further studies have already shown.

Sensitivity (98.4%) and specificity (100.0%) of the OtCM blister packages were convincing. Also robustness was shown under almost all conditions. Only the blisters stored at 2–8 °C showed a diminished accuracy rate (80.0%). With the relatively small number tested this is most probably an artefact, but it will be the subject of further studies.

Future perspectives

Due to the elaborate design of the RFID labels and the promising results of our studies, we believe that the OtCM blister packages have the capability to become a new "gold standard" as a method for compliance measurement in clinical and outcome studies. In future the RFID labelling will be done automatically by using a pick-

Table 1. Accuracy and sensitivity of the functioning OtCM-blisters under different conditions

	Laboratory conditions	Robustness					Total
		2–8 °C		40 °C	Drop-test	Real-life conditions	
Number of removals (n)	500	50	40*	50	50	140	790
Number of registered removals	490	50	40*	49	48	140	777
Number of correct registered times	479	40	40*	49	48	140	756
Accuracy (%)	95.8	80.0	100.0*	98.0	96.0	100.0	95.7
Sensitivity (%)	98.0	100.0	100.0*	98.0	96.0	100.0	98.4

(*Results calculated by disregarding the data of 1 damaged blister package)

and-place technology. This will further enhance the accuracy and functionality, making the OtCM system more accurate and convenient for measuring compliance with oral medication than any other existing method.

A further mission of TCG is to develop the OtCM system in a way that it can be applied to existing blister packages during the industrial manufacturing process. This will result in a mass production of intelligent blister packages and thus allow compliance measurement right out of the standard blister package. A "system-in-foil" application (electronics, power supply in the form of printed batteries and organic electronic circuitry embedded in the aluminium foil of the blister package) will minimise costs.

By using a DataGator™ (TCG's telemedicine device) operated by the patient, real-time compliance measurement will be feasible and will allow the instantaneous intervention of the healthcare provider in the outpatient setting. The DataGator can also be used to transfer information from medical diagnostic devices, such as blood pressure monitors, glucose meters, ECG recorders and others, to the database server.

The real-time monitoring and correlation of compliance and outcome data will enable caregivers, such as physicians and pharmacists, to make prompt and more valid drug therapy decisions. Increased medication and patient safety, and decreased costs of care are to be expected. ■

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