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# Recurrence of Adverse Drug Reactions following Inappropriate Re-Prescription

## Better Documentation, Availability of Information and Monitoring are Needed

*Carolien M.J. van der Linden,*[1] *Paul A.F. Jansen,*[2] *Rob J. van Marum,*[2,3] *René J.E. Grouls,*[1] *Erik H.M. Korsten*[1,4] and *Antoine C.G. Egberts*[2,5]

1 Catharina Hospital, Eindhoven, the Netherlands
2 University Medical Centre Utrecht, Utrecht, the Netherlands
3 Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands
4 Eindhoven University of Technology, Eindhoven, the Netherlands
5 Utrecht Institute for Pharmaceutical Sciences, Utrecht, the Netherlands

## Abstract

Adverse drug reactions (ADRs) are a common, and often preventable, cause of hospital admission, especially in the elderly, and can occur during hospitalization.

In this current opinion article, we present three cases of recurrence of a serious ADR due to re-prescription of a withdrawn medication that highlight the need for a system to prevent the undesirable re-prescription of medications withdrawn because of an ADR. In addition, we describe an electronic system that could help prevent undesirable re-prescription following an ADR. Such a system should document ADRs systematically at the patient level, make this information available to relevant healthcare providers and the patient, and flag re-prescription of the offending drug. The effectiveness and cost effectiveness of such a system would need to be determined.

Adverse drug reactions (ADRs), defined as 'appreciably harmful or unpleasant reactions, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product',[1] are a common, and often preventable, cause of hospital admission, especially in elderly people.[2] They are also common during hospitalization.[3] In an earlier study, we showed that ADRs occurring during hospitalization and requiring withdrawal of the causative drug were poorly communicated to general practitioners (GPs) and primary-care pharmacists, and that only 22% of the ADRs mentioned in discharge letters were incorporated into GPs' patient files.[4] The rate of re-prescription of medication withdrawn during hospitalization because of an ADR was 27% in the first 6 months after discharge. Poor documentation and communication probably contributed to this high rate of re-prescription. Although re-prescription of a drug after an ADR may sometimes be appropriate, we want to highlight the need for improved documentation and communication regarding ADRs, and for a

system for alerting doctors and pharmacists if a previously withdrawn medication is re-prescribed. To illustrate this, we present three cases of recurrence of a serious ADR due to re-prescription of a withdrawn medication from two hospitals in the Netherlands: University Medical Centre, Utrecht, and Catharina Hospital, Eindhoven. In addition, we propose a system to improve the documentation and communication of ADRs and to optimize alerting in the event of re-prescription, independent of the healthcare setting.

## 1. Case Reports

### 1.1 Case 1

A 53-year-old woman with a history of pneumonia, asthma, ulcerative colitis and allergy to NSAIDs (two events in 15 years) complained of abdominal pain during the weekend. The GP on duty (not the patient's GP) prescribed the NSAID diclofenac as a suppository. Shortly after taking a single dose, the patient developed exanthema and became dizzy. Her husband called an ambulance and on its arrival the patient was hypotensive. She was treated with intravenous adrenaline (epinephrine) and dexamethasone for suspected anaphylactic shock and admitted to hospital, where she made a rapid recovery. Her abdominal pain was caused by pancreatitis. The GP on duty had missed the information regarding her allergy to NSAIDs in her medical records. Moreover, although it was possible to register allergies in the hospital's electronic medication prescription program, this was not done before, during or after this most recent hospitalization.

### 1.2 Case 2

An 82-year-old man with a history of Parkinson's disease, transurethral resection of the prostate, cataract extraction and Meniere's disease had a urinary tract infection complicated by delirium, for which the GP prescribed haloperidol. Within a few days the patient's Parkinson's disease symptoms worsened considerably and hospitalization was necessary. His medication on admission was pergolide 1 mg four times daily, selegiline 5 mg twice daily, levodopa/carbidopa 100/25 mg twice daily and haloperidol twice daily (0.5 mg in the morning and 0.25 mg in the evening). During hospitalization, haloperidol was withdrawn and the dosage of levodopa/carbidopa was increased to 100/25 mg four times daily, which diminished the Parkinson's disease symptoms. The discharge letter from the hospital to the GP mentioned the aggravation of Parkinson's disease symptoms with haloperidol, and advised the prescription of clozapine or quetiapine instead of haloperidol in the event of delirium. However, 3 months after discharge, the same GP prescribed haloperidol for agitation, which again caused worsening of Parkinson's disease symptoms. After consultation with the geriatrician, haloperidol was withdrawn and quetiapine was started. The patient's Parkinson's disease symptoms improved and his agitation diminished. The GP reported he was not aware of the earlier advice not to re-prescribe haloperidol.

### 1.3 Case 3

An 85-year-old woman with a history of hypertension, diabetes mellitus, nodular struma, breast cancer (6 years previously) and mild hyperparathyroidism was referred to a geriatric ward by her GP because of delirium. She was taking insulin, digoxin, tamoxifen, amiloride and hydrochlorothiazide. On admission, she had hypercalcaemia (3.06 mmol/L corrected for serum albumin); her renal function was normal. Hydrochlorothiazide was withdrawn because it may have contributed to hypercalcaemia and the patient was treated with intravenous hydration and pamidronate. Serum calcium decreased to 2.49 mmol/L and the delirium resolved. The discharge letter to the GP mentioned the probable contribution of hydrochlorothiazide to the development of hypercalcaemia. Over the next 10 months the patient was treated with cinacalcet and her serum calcium remained stable at 2.70 mmol/L. She was then readmitted to hospital because of delirium. On admission, the serum calcium concentration was 3.44 mmol/L and her renal function was impaired. The GP had

re-prescribed hydrochlorothiazide, which might have contributed to the recurrence of hypercalcaemia. Discontinuation of hydrochlorothiazide and intravenous hydration led to a decrease in serum calcium and to resolution of the delirium.

## 2. Discussion

These case reports illustrate that poor documentation of ADRs and inadequate availability of this information to relevant healthcare providers, together with the lack of an automated alert for re-prescription of a previously withdrawn medication, may lead to the possibly inadvertent re-prescription of an offending medication and to the recurrence of ADRs.

The impact of the re-prescribed drugs is not entirely clear cut in our cases and multiple factors may have contributed to the ADRs. In case 1, we cannot be entirely sure the patient experienced an anaphylactic shock, although she was known to have an allergy to NSAIDs. This allergy was not documented in the electronic medication prescription programme of the hospital and the GP on duty was not aware of this allergy. In this case, insufficient documentation probably led to re-prescription. In case 2, the patient's reaction to haloperidol was well documented in the hospital. The clinical symptoms and time-course suggest a causative relationship between haloperidol and aggravation of Parkinson's disease symptoms. In this case, the GP was advised not to re-prescribe haloperidol, and re-prescription seems to result from insufficient or absent alerting. In case 3, multiple factors contributed to hypercalcaemia: hyperparathyroidism, hydrochlorothiazide and, on readmission, impaired renal function. In this case, the possible contribution of hydrochlorothiazide to hypercalcaemia was documented in the hospital and it was mentioned in the 'clinical course' section of the discharge letter but not in the 'conclusion' or 'advice' section of the discharge letter. As in the other two cases, information about the ADR was not communicated to the pharmacist. In this case, the information was not available to all relevant healthcare professionals, and alerting to possibly undesirable re-prescription was not carried out.

Re-prescription of drugs after an ADR may be appropriate and acceptable in some cases, e.g. when the dose had been too high, causing a toxic effect, when the ADR could have been prevented by the co-prescription of another drug, or when a previous susceptibility factor is no longer present. It may also be appropriate to use a lower dose in combination with a drug with the same treatment goal but with a different mechanism of action and different adverse effects.[5]

While pharmacovigilance is quite well developed in terms of regulatory requirements for the pharmaceutical industry, it is primarily geared towards product surveillance and liability rather than surveillance and therapeutic decision making at the patient level. To improve pharmacovigilance at the patient level, we propose an electronic system to prevent the undesirable re-prescription of medications previously withdrawn for causing ADRs, or to propose measures to prevent recurrence of the ADR in case of re-prescription. This system has three essential elements.

1. *Documentation*: All ADRs, as defined above, should be documented systematically and in a standardized manner. This registration minimally needs to consist of the name of the prescribing doctor; date of occurrence of the ADR; name, dose and duration of the suspected drug; and description of the ADR. The causality and seriousness of the ADR should be documented. Causality should preferably be determined with an algorithm, e.g. Naranjo[6] or Kramer et al.[7] and seriousness could be classified according to European Medicines Agency definitions: an ADR is serious if fatal, life-threatening, requiring inpatient hospitalization or prolongation of existing hospitalization, or resulting in persistent or significant disability.[8]
2. *Availability*: The systematically documented information should be available and accessible to the patient and, with the patient's permission, to all relevant healthcare providers, including hospital specialists, GPs and pharmacists.
3. *Alerting*: Prescribed medication should be constantly monitored and the pharmacists/

GPs/patients should be alerted if a previously withdrawn medication is re-prescribed.

The electronic clinical decision support module we are currently developing incorporates these elements, and future studies will test its usefulness in patient care, i.e. whether it prevents the re-prescription of previously withdrawn medications, and its cost effectiveness. During the development of this module, we paid particular attention to the timing and design of alerts, to minimize information overload and overriding, and to ensuring the confidentiality of patient data.

## 3. Conclusions

We have presented three cases that highlight the need for a system to prevent the undesirable re-prescription of medications withdrawn because of an ADR. Such a system should document ADRs systematically at the patient level, make this information available to relevant healthcare providers and the patient, and flag re-prescription of the offending drug. The effectiveness and cost effectiveness of such a system would have to be determined since we currently do not know how often ADRs occur because of inappropriate re-prescription after a previous ADR.

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Correspondence: Dr *Carolien M.J. van der Linden*, Catharina Hospital, P.O. Box 1350, 5602 ZA, Eindhoven, the Netherlands.
E-mail: carolien.vd.linden@cze.nl