The development and piloting of “ATTEND DR”, a clinical teaching tool to identify and prioritise potential causes of adverse drug reactions

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KEYWORDS

MeSH terms

Drug-related side effects and adverse reactions, Pharmacovigilance, Education, Teaching, Clinical competence

Other

Mnemonic

ABSTRACT

Background

The identification, management, and reporting of adverse drug reactions are integral to clinical practice and education; however, undergraduate teaching related to adverse drug reactions may be inadequate for practice. Existing methods of causality assessment have a number of limitations in relation to clinical teaching, e.g. they do not deal well with the concurrent use of other medications.

Objective

To develop and pilot a teaching tool to guide students through the process of identifying and prioritising potential causes of an adverse drug reaction.

Setting

University based School of Pharmacy, Australia: an undergraduate Quality Use of Medicines course.

Method

A contrived acronym (mnemonic) was developed from causality assessments and discussions with practitioners. The acronym ATTEND DR (abnormality, taken, timeline, evidence, nothing else?, dose, dechallenge, and rechallenge) was piloted in workshops that focussed on adverse drug reactions and their management. Students' responses to: "What did you find most valuable about today's workshop?" and "How could we improve?" were analysed.

Results

All attendees responded (65/65). Students indicated that the ATTEND DR acronym was easy to remember, and facilitated causality assessment in a clinical context, due to an easily followed, step-by-step, comprehensive process that was easy to remember. More practice case studies were requested.

Conclusion

The ATTEND DR acronym was designed to address limitations of the existing methods of causality assessment in relation to clinical teaching and preparation of students for future clinical roles.

Students responded favourably to its introduction, commenting that it was easily remembered and provided a comprehensive, clinically orientated, step-by-step process.

Experiences in Teaching and Learning

The development and piloting of “ATTEND DR”, a clinical teaching tool to identify and prioritise potential causes of adverse drug reactions

What was done

A teaching tool in the form of a contrived acronym was developed to help students identify the most likely cause of an adverse drug reaction (ADR) or potential causes that could be modified to manage the ADR, or both. Edwards and Aronson described an ADR in the context of clinical practice as “an appreciably harmful or unpleasant reaction, 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

The literature links ADR identification with algorithms for causality assessment and expert opinion.²⁻⁹ Therefore to develop the tool, causality assessments⁷⁻⁹ were reviewed to identify common or relevant factors, and the opinions of health practitioners with considerable experience in identifying ADRs were sought. Each practitioner had at least 20 years of clinical experience and held a senior or specialist clinical position at the time of the study. They comprised clinical pharmacists, who were also university academics, and a general practitioner with clinical teaching experience. Both authors had experience in clinical pharmacy or clinical pharmacology, and pharmacovigilance at a state or national level. The discussions with the health practitioners were also used to identify a potential process for determining possible causes of an ADR and discriminating between these causes.

The initial acronym, developed in 2012, was TRACED (timeline, rechallenge, abnormality, cannot be another cause, evidence, dechallenge/dose). Informal student feedback and observation of the students’ application of the algorithm identified that the order of the letters needed to be altered. While most students could remember the factors, the order of the factors did not match with their importance or the experts’ process resulting in poor application. Revision resulted in the acronym

ATTEND DR (abnormality, taken, timeline, evidence, nothing else?, dose, dechallenge, rechallenge).

Each word relates to a more detailed explanation for its application (Table 1).

The identification and management of ADRs was the focus of two ADR lectures lasting one hour each and an ADR workshop lasting 2.5 hours in a Quality Use of Medicines course. The lectures presented the theory of causality assessment; the advantages and disadvantages of the Naranjo algorithm,⁸ the World Health Organisation (WHO) ADR probability scale,⁹ and expert opinion; and introduced the ATTEND DR acronym as a beta-version of a tool to assess causality in a clinical context. Strategies for managing ADRs were taught at the end of the second lecture and were related back to the most likely, and other, potential causes. Identifying the most likely cause of the ADR or the drug that can be altered with the least risk to the patient is important as clinical management generally involves changing only one drug at a time. If only one drug is changed then it is easier to identify if it was the cause of the ADR while limiting unnecessary changes that might harm the patient.

The workshop was facilitated by two academic staff who were available to assist students with the application of lecture content to clinical cases. The cases progressed from simple (single medication, no confounding factors) to more complex (polypharmacy, confounding factors) scenarios, with emphasis on identifying the most likely cause of the ADR. The workshop was held in a teaching space with a capacity of 40 students and repeated as 80 students were enrolled in the course. Each student had access to a personal computer with internet connections to drug information resources via the university's library.

Why it was done

Adverse drug reactions (ADRs)¹ are common^{14,15} and costly.^{16,17} In clinical practice they not only need to be identified, they also need to be managed. The identification, management and reporting of ADRs are integral parts of clinical practice and education. However, undergraduate teaching related to ADRs may be inadequate for practice.^{18,19} Reports related to the teaching of ADRs tend to

focus on pharmacovigilance and spontaneous reporting systems,^{20,21} and not the identification or management of ADRs in a clinical setting. In addition to this, the teaching of pharmacovigilance in some undergraduate programs is low.^{19,20}

Causality assessment is central to both the identification and management of ADRs. Methodologies for causality assessment include expert judgement/global introspection, operational algorithms, and probabilistic approaches.^{7,22} Each has advantages and limitations, especially in a teaching context. Expert judgement/global introspection, while considered in several studies as the standard against which to measure other methods,^{4-6,23} is subjective and lacks standardisation,³ and students have limited expertise. While promising in terms of validity, the development of probabilistic measures requires knowledge of prior odds and likelihood ratios, as well as complex calculations.⁷ As prior odds and likelihood ratios may not be available, and due to the complexity of the calculations, probabilistic measures are not currently relevant to either teaching or general clinical practice. Algorithms are easy to use and can produce a consistent answer,⁷ therefore they seem the obvious approach to teaching students how to identify the potential cause(s) of an ADR. However the ability to produce a consistent answer does not necessarily mean that they are valid.²⁴ Algorithms may not deal well with confounding variables, e.g. the presence of underlying disease, concomitant use of other medications, absence of reports of that particular ADR, simultaneous cessation of other medications/treatments, and unknowns.^{4,6} Algorithms also lack the flexibility to include additional information, and may not be able to identify ADRs resulting from drug-drug interactions.⁷ In clinical situations confounding variables and drug-drug interactions are not uncommon, and a strategy to manage the ADR is required. Identifying the most likely cause is the foundation for the development of an appropriate management strategy. At the School of Pharmacy, Griffith University undergraduate teaching related to ADRs included the identification, reporting, avoidance, and management of ADRs, as well as their classification using both the Naranjo algorithm⁸ and the World Health Organisation (WHO) ADR probability scale.⁹ Students were capable of applying these tools, but when a number of medications were taken concurrently, they had difficulty identifying the

medication most likely to be responsible for the ADR or the medication that should be adjusted or ceased first. This was because, when causal algorithms were applied to multi-medication regimens, the maximum level of causal probability associated with the regimen was often reached by more than one medication. Given that 74% to 78% of ADR reports listed more than one medication,^{5,6} and the need to help students develop ADR identification and management strategies that would prepare them for and be useful in their future roles, we looked to clinical practice to help overcome this difficulty.

While no true gold standard for causality assessment of ADRs exists,^{3,7} expert opinion has been considered to be superior to other methods.^{5,6} Expert opinion can form the basis of a management plan as it may be able to single out a medication. However, the inter-rater variability of expert opinion/global introspection needs to be addressed. A guided series of questions has been used to optimise efficiency and enhance standardisation of causality assessment.² Arimone et al. recommended a combination of causal criteria in a standardised procedure to increase the reliability of global introspection.²² This was the basis for the development of the teaching tool which also needed to be easy to remember and apply. Due to the improved recall, and concept application and analysis associated with the use of acronyms,²⁵ it was decided that the criteria and procedure should be based around a contrived acronym (mnemonic), i.e. one associated with an apt name or description.

Where and when it was done

In 2012 and 2013 the School of Pharmacy offered a three year undergraduate Bachelor of Pharmaceutical Science program; a prerequisite for the 1.5 year postgraduate Master of Pharmacy program. In the second year of the Bachelor of Pharmaceutical Science program, students were taught the mechanisms of ADRs. In the final semester of the third year, the Quality Use of Medicines course expanded this knowledge utilizing more clinical context. The lectures that

implemented the ATTEND DR acronym were held in week 3 of a 13 week semester and the workshops in week 4.

How it was evaluated

Observations made by teaching staff were used to evaluate the application of the ATTEND DR acronym. Staff actively scanned for students that might be having difficulties, as well as students formally requesting help, to identify problems associated with the application of the acronym.

Student feedback was obtained via a survey distributed to the 65 students (out of the 80 enrolled) that attended the optional workshops. The survey comprised two questions: “What did you find most valuable about today's workshop? (e.g. ATTEND DR approach)” and “How could we improve?” Responses were read through by each author separately to identify the most commonly occurring ideas. The authors discussed these ideas and agreed without dissent on the themes that best represented them. The authors then jointly categorised the responses into these themes, manually coding the data based on the consensus achieved. Institutional Human Research Ethics Committee approval was obtained PHM/09/13/HREC.

What was found

Teaching staff observed that the use of the revised tool appeared to result in students effectively differentiating the most likely cause of an ADR from other potential causes to a degree where further adjustments were not considered necessary.

Response to the survey from the workshop attendees (n=65) was 100%. Survey feedback concerning the updated tool was based around five themes:

The acronym was easy to remember;

“Very easy to remember.”

“Makes it easy to remember for a clinical case.”

"Easy to understand and remember especially for exams."

The step by step process for identification provided clear guidance to single out the most likely cause when causality was potentially multifactorial;

"Good step to step exercise."

"Step by step and very comprehensive. Makes problem solving easier."

"Useful when patient is taking so many medications and how to find a potential cause!"

The acronym was comprehensive or holistic, or both in its ability to encompass factors related to ADRs;

"I feel that the ATTEND DR approach is very comprehensive and forces the investigation of given evidence to lead to a practical and safe resolution to the problem presented."

"I think the ATTEND DR method is very helpful and well rounded. It forces you to assess the whole situation including the disease states and drugs."

"Cover all the points with a practical case."

Orientated towards clinical practice;

"Help in analysing a clinical case. It ensures that you cover all bases of possible causes of ADRs."

"Good way of analysing the problem with patient and possible outcome if properly treated. Very clinical orientated with more practice."

As noted above more practice based on clinical case studies was preferred.

"More practice please!"

"More clinical cases please."

“Once we understand the method it was quite a useful way to go through the patient’s case and determine what was the cause with MORE PRACTICE needed.”

The ATTEND DR acronym facilitates the assessment of ADRs in cases that include confounding factors several of which are recognised shortcomings of algorithms.^{4,6} Based on the observations made by staff this is probably due to increased scrutiny of temporal relationships (Timeline), reported incidence of the ADR (Evidence) and alternative causes (Nothing else?) including other medications, complimentary/alternative medications, lifestyle, underlying disease and drug-drug interactions.

Developing the acronym was the most difficult part of the process. By third year students have learnt a number of acronyms. The TRACED acronym contained letters that were present in other acronyms used in clinical teaching but the same letter did not necessarily represent the same word or concept. Some students recalled the wrong words or concepts because of this. Developing a word or words that contain all the necessary letters; ensuring consistency across acronyms; and relating the letters and the final word or words intuitively to the topic, was a complex task. Students’ application showed that the order of the letters was as important as the letters themselves. The most rewarding aspect was observing the students’ application of the ATTEND DR acronym.

Students’ comments indicated that the ATTEND DR acronym was easy to remember, and made problem solving easier, especially in a clinical context, due to a step-by-step, comprehensive process that could be easily followed. The request for more clinical cases indicated that learning through practical application was important to students. No further alterations to the ATTEND DR acronym are planned. Additional practice cases have been added to the course website.

Research relating to the teaching of ADRs is limited. Literature searches revealed that ADR teaching focussed on how and what to report,¹⁹⁻²¹ and the application of the Naranjo algorithm,⁸ rather than the clinical context where managing the ADR is an integral aspect of providing patient care.

Rovers et al. noted that the ability of pharmacy students to integrate all information simultaneously when identifying medication therapy problems in a clinical situation was limited and suggested that guided tools may assist with skill development.²⁶ Based on our observation and student comments it appears that identification of potential causes and the most likely cause of an ADR, in a situation with confounding factors, was improved by the step-by-step approach facilitated by the ATTEND DR acronym.

This was a pilot study of the application of the ATTEND DR acronym in a relatively small number of pharmacy students at one Australian university; as such it may not be generalizable to other populations. We recognise that the acronym is based on the English language, however the step-by-step process is universal. Also acknowledged is the conflict of interest associated with the development, teaching and evaluation of the ATTEND DR acronym.

While students' identification of the most likely cause of an ADR and other potential causes appeared to improve, this was not measured directly. Future research needs to evaluate the impact of the ATTEND DR acronym using an objective measure and whether the use of the acronym is beneficial to students in other health disciplines, e.g. medicine and nursing, and at other institutions, and to recently registered health professionals who may have limited experience with ADRs. This may occur in the not too distant future as its inclusion in inter-professional or medical teaching activities is currently under discussion at our institution.

Assessing whether using the ATTEND DR acronym increased agreement between practising health professionals due to a more standardised procedure as recommended by Arimone et al.²² could be another potential avenue for future research. However, as some criteria may always be subjective,

and therefore associated with inter-rater variability,²² complete agreement is unlikely. The benefit of the standardised process based on the ATTEND DR acronym for health professionals is that it may decrease the likelihood that an important factor will be overlooked when assessing causality and facilitate the transition between the identification of an ADR and its management.

Final take away points

The teaching of pharmacovigilance is low and focusses on ADR reporting. Tools currently used for causality assessment have several limitations in relation to clinical teaching as they do not adequately address confounding factors or facilitate the development of a strategy to manage the ADR. While developing the ATTEND DR acronym was complex its implementation was straightforward, requiring no additional resources compared to previous teaching. Students reported that the ATTEND DR acronym was easy to remember, and facilitated ADR causality assessment in a clinical context, due to an easily followed, step-by-step, comprehensive process.

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CONFLICT OF INTEREST

The authors developed the ATTEND DR acronym and taught the ADR module of the Quality Use of Medicines course.

REFERENCES

1. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356(9237):1255-1259.
2. Collet JP, MacDonald N, Cashman N, Pless R. Monitoring signals for vaccine safety: the assessment of individual adverse event reports by an expert advisory committee. *Bull World Health Organ*. 2000;78(2):178-185.
3. Théophile H, Arimone Y, Miremont-Salamé G, et al. Comparison of three methods (consensual expert judgement, algorithmic and probabilistic approaches) of causality assessment of adverse drug reactions. *Drug Saf*. 2010;33(11):1045-1054.

4. Macedo AF, Marques FB, Ribeiro CF, Teixeira F. Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel, according to different levels of imputability. *J Clin Pharm Ther.* 2003;28(2):137-143.
5. Macedo AF, Marques FB, Ribeiro CF. Can decisional algorithms replace global introspection in the individual causality assessment of spontaneously reported ADRs? *Drug Saf.* 2006;29(8):697-702.
6. Macedo AF, Marques FB, Ribeiro CF, Teixeira F. Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel. *Pharmacoepidemiol Drug Saf.* 2005;14(12):885-890.
7. Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions. *Drug Saf.* 2008;31(1):21-37.
8. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30(2):239-245.
9. World Health Organization. The use of the WHO-UMC system for standardized case causality assessment. *Uppsala: The Uppsala Monitoring Centre* 2005.
10. Théophile H, André M, Arimone Y, Haramburu F, Miremont-Salamé G, Bégaud B. An updated method improved the assessment of adverse drug reaction in routine pharmacovigilance. *J Clin Epidemiol.* 2012;65(10):1069-1077.
11. Al-Niaimi F. Drug eruptions in dermatology. *Expert Rev Dermatol.* 2011;6(3):273-286.
12. Yu EW, Finkelstein JS. Bone density screening intervals for osteoporosis: one size does not fit all. *JAMA.* 2012;307(24):2591-2592.
13. *Australian Medicines Handbook 2015.* Adelaide: Australian Medicines Handbook Pty Ltd; 2015.
14. Taché SV, Sönnichsen A, Ashcroft DM. Prevalence of adverse drug events in ambulatory care: a systematic review. *Ann Pharmacother.* 2011;45(7-8):977-989.
15. Martins A, Giordani F, Rozenfeld S. Adverse drug events among adult inpatients: a meta-analysis of observational studies. *J Clin Pharm Ther.* 2014;39(6):609-620.
16. Meier F, Maas R, Sonst A, et al. Adverse drug events in patients admitted to an emergency department: an analysis of direct costs. *Pharmacoepidemiol Drug Saf.* 2015;24(2):176-186.
17. Gyllenstein H, Hakkarainen KM, Hägg S, et al. Economic impact of adverse drug events – A retrospective population-based cohort study of 4970 adults. *PLoS One.* 2014;9(3):e92061.
18. Tobaigy M, McLay J, Ross S. Foundation year 1 doctors and clinical pharmacology and therapeutics teaching. A retrospective view in light of experience. *Br J Clin Pharmacol.* 2007;64(3):363-372.
19. Generali J. Adverse Drug Event Reporting: Awareness Is Not Enough. *Hosp Pharm.* 2014;49(2):110-111.
20. Smith MP, Webley SD. Pharmacovigilance teaching in UK undergraduate pharmacy programmes. *Pharmacoepidemiol Drug Saf.* 2013;22(3):223-228.
21. Cox AR, Marriott JF, Wilson KA, Ferner R. Adverse drug reaction teaching in UK undergraduate medical and pharmacy programmes. *J Clin Pharm Ther.* 2004;29(1):31-35.
22. Arimone Y, Miremont-Salamé G, Haramburu F, et al. Inter-expert agreement of seven criteria in causality assessment of adverse drug reactions. *Br J Clin Pharmacol.* 2007;64(4):482-488.
23. Théophile H, André M, Miremont-Salamé G, Arimone Y, Bégaud B. Comparison of three methods (an updated logistic probabilistic method, the Naranjo and Liverpool algorithms) for the evaluation of routine pharmacovigilance case reports using consensual expert judgement as reference. *Drug Saf.* 2013;36(10):1033-1044.
24. Doherty MJ. Algorithms for assessing the probability of an adverse drug reaction. *Respir Med CME.* 2009;2(2):63-67.

25. Saber JL, Johnson RD. Don't throw out the baby with the bathwater: verbal repetition, mnemonics, and active learning. *J Marketing Educ.* 2008;30(3):207-216.
26. Rovers J, Miller MJ, Koenigsfeld C, Haack S, Hegge K, McCleary E. A guided interview process to improve student pharmacists' identification of drug therapy problems. *Am J Pharm Educ.* 2011;75(1):Article 16.

Table 1. How to apply the ATTEND DR acronym

Acronym	Description/Application	Example
A - Abnormality/ adverse effect	What is the ADR? Is the evidence behind it subjective (patient report) or is it objective (observable)?	Patient reports muscle pain (subjective). Raised creatine kinase indicates muscle breakdown (objective).
T – Taken (suspected medication)	Did the patient take the medication? (Do not assume because a patient was prescribed a medication that they have taken it or taken the prescribed dose)	Non-compliant patient.
T – Timeline	Check whether there were symptoms of the ADR before or after the medicine was taken. (There may be a pre-existing condition) Does the timing fit with the natural history of the adverse effect?	Patient has no previous history of muscle pain. Seizures during the administration of an intravenous infusion is almost conclusive. ¹⁰ Exanthematous rashes usually appear within 14 days of initial exposure ¹¹ therefore a recent exposure is the most likely cause. Osteoporosis can take several years to become evident ¹² therefore a single recent exposure is unlikely to be the cause.
E – Evidence	Do symptoms match with the ADRs noted in the literature? What is the frequency in the literature?	The patient reports diarrhoea which is a listed adverse effect of metformin. ¹³ The frequency of hepatotoxicity with methotrexate is common (>1%) while with carbamazepine it is rare (0.1%) ¹³ therefore the cause is more likely to be methotrexate (although carbamazepine should not be completely ruled out).
N – Nothing else?	Is there any other cause of ADR? (For example, other medications, complementary/alternative medications, lifestyle, underlying disease) Is there a pharmacokinetic drug-drug or drug-disease interaction that could result in increased blood levels? Is there a pharmacodynamic drug-drug or drug-disease interaction that could result in increased symptom levels?	The patient has muscle pain and is taking a statin but has recently joined a gym. The patient is taking simvastatin and has started drinking grapefruit juice with breakfast. ¹³ The patient is taking fluoxetine and commences domperidone and develops torsades des points due to a further increase in QT interval. ¹³
D - Dose	Does the side effect worsen if the dose is increased; or lessen if the dose is decreased? Check if the dose is too high, especially if the patient is a child or elderly or has renal or liver impairment.	The dose of statin is increased and the muscle pain worsens. A patient with renal impairment (Creatinine Clearance 10-15ml/min) is prescribed trimethoprim 300mg daily when the recommended dose is 150mg daily. ¹³
D – Dechallenge	Does the adverse effect cease if the medication is stopped? (An important aspect of this is to identify the medication most likely to have caused the ADR as its cessation	The patient ceases a statin and his muscle pain disappears and his creatine kinase returns to normal.

or a decrease in its dose is often the first step in the management of the ADR)

R – Rechallenge

Does the recommencement of the medication result in the same symptoms? (This is avoided if possible when the ADR is serious or life-threatening especially when alternative medications are available. If the side effect is minor and the medication is considered to be a superior choice then a rechallenge might be appropriate.)

A patient reporting a penicillin allergy might be rechallenged (with appropriate emergency care available) if they have a life threatening bacterial infection that is sensitive to nothing other than penicillin.

ADR = Adverse drug reaction