BNF Publications

New BNF and BNF *for Children* Interactions

Frequently Asked Questions

August 2017 – version 1

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Product & Methodology details

Why has the interactions content for BNF and BNF for Children changed?

Following the change to the systems and data structures that underpin the BNF content, which began in 2015, we are able to revisit how we present interactions in the BNF Publications.

We know from listening to users that the interactions content was becoming increasingly difficult to access. We were also aware that the nature of the way interactions were studied had changed, with regulatory authorities providing more guidance around predicting interactions. In addition, the BNF is committed to making the sources of its recommendations more transparent and so the time had come to re-write the interactions content to address all of these points.

What are the benefits of the new version?

The biggest change in this rewrite is the acknowledgment that the predictions behind interactions are now much more reliable. Therefore, predicted interactions, where the result is substantiated by the known effects of the drugs and likely to result in a clinically important effect, are now more thoroughly and consistently covered.

In our improved content, finding interactions will be quicker and simpler as a result of:

- **A consistent approach to pharmacodynamic interactions**. In print, creating tables of drugs known to have certain pharmacodynamics effects ensures coverage is more consistent. Digital platforms provide the same information but as messages between drug pairs.
- **More user-friendly access to the information**. Notes that were previously in the BNF main text are either included in Appendix 1 or signposted from Appendix 1 so you only have one place from which to start your search for interactions information.
- **A more systematic approach to actions**. Actions that should be taken as a result of an interaction are now more consistently present and are included whenever a manufacturer recommends avoiding the combination, or changing the dose.
- **Levels of evidence**. The addition of this information illustrates the strength of the information underpinning our recommendations, in line with the work to make this evident across the whole of the BNF.
- **Assessments of severity**. Including information about the possible severity of an interaction will help clinicians distinguish between interactions that may result in highly detrimental effects and interactions that may cause minimal inconvenience to a patient.

Is there any information that was in the old version that won't be in the new version?

Yes. BNF interactions now do not generally contain information in the following areas:

1. Interactions where the effect is intentional and where the patient will be closely monitored – for example, the use of opioids alongside anaesthetics.
2. Interactions where the interaction is dependent on the patient developing a side effect of a drug – for example, drugs that cause diarrhoea as a side effect are not included as interacting with contraceptives. If the adverse effect is considered important an appropriate warning has been included within the cautions for that drug.
3. Interactions based on case reports where there is no known mechanism for the effect and use over time suggests that no interaction usually develops – for example warfarin and disopyramide. Interactions based on case reports have also been left out when the data has been superseded by better evidence (e.g. a formal study) that suggests a lack of interaction.
4. Cases where the manufacturer advises that a combination should be avoided because the use of that combination has not been studied – this most commonly occurs with antineoplastics.
5. When pharmacokinetic studies suggest that the effect of the interaction is only slight – this is because a slight change in exposure is unlikely to be clinically important.
6. Where a drug has the same effect or an opposing effect as an adverse effect of another drug – for example, in the past, an interaction would have been included if a manufacturer stated that a patient with diabetes taking an antidiabetic drug that reduces blood glucose should not be given a drug that reduces blood glucose as a side-effect. This information has been included under the cautions for that drug.
7. Interactions where a theoretical prediction made by a manufacturer is not supported by evidence – for example, a number of manufacturers consider ciprofloxacin to be a CYP3A4 inhibitor; while this may be the case in vitro, data from the clinical use of ciprofloxacin suggests that this does not result in a clinically meaningful effect. Another example, of particular note, is rifabutin, which is listed by many manufacturers as a potent inducer of CYP3A4: the available clinical data suggests that rifabutin is only a weak or moderate inducer of this isoenzyme.

How did you undertake the re-writing of the interactions?

We worked with the expert editorial team that write *Stockley's Drug Interactions* to draft a new policy for BNF interactions content that was shared with a working group drawn from members of the BNF Joint Formulary Committee. The policy was approved in principle and a pilot re-write of the content undertaken. This led to some small adjustments to the policy before the full re-writing began.

Firstly we wrote interactions for all of the drugs in the BNF, using our standard 3-step approach of writing the content, independently reviewing the content and then independently approving the content as fit for publication. Once this process was complete we compared the old content to the new content to ensure nothing critical had been overlooked or omitted.

Only after completing this thorough review process did we sign the content off as ready for inclusion in the BNF Publications.

How has *Stockley's Drug Interactions* influenced the content of the BNF interactions?

We have used the understanding of the clinical importance of the effects of drugs on various cytochrome P450 isoenzymes, which we derived from *Stockley's Drug Interactions*, to apply some system to manufacturer's predictions. However, we have not used the advice created by the team behind that product: the BNF continues to reflect the manufacturer's advice.

The BNF is intended as a digest for rapid reference and therefore interactions are included, as they always have been, as an indication of whether or not a certain drug pairing is likely to result in a significant interaction. The content is, by necessity, not as in-depth or comprehensive as that included in *Stockley's Drug Interactions*, which remains a useful specialist reference source to supplement the BNF information.

Is there any difference between the interactions in BNF and BNF *for Children*?

No, the full content remains the same in both publications.

Have all versions of the BNF products been updated with the new interactions?

All print and digital products based on the new BNF structure will be updated with the new BNF interactions. BNF 74 and BNFC 2017-2018 will be distributed in September with the new interactions. MedicinesComplete and the new BNF app will be updated with the new interactions in the coming months. Legacy products will not be updated with the new interactions; these products will show the existing interactions until their retirement.

Features documentation

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How do I assess the importance of an interaction without the black dot feature?

The black dot only allowed for two levels of severity to be represented. In the new content, there are four levels of severity – this is expressed by the use of words, rather than symbols.

The first three levels of severity are mild, moderate and severe, and represent the possible worst-case outcome if the interaction is not managed. Unknown is used rarely but included where there is insufficient information to establish what the outcome of a predicted interaction might be. The full definitions are as follows:

- SEVERE – the result may be a life-threatening event or have a permanent detrimental effect.
- MODERATE – the result could cause considerable distress or partially incapacitate a patient; they are unlikely to be life-threatening or result in long-term effects.
- MILD – the result is unlikely to cause concern or incapacitate the majority of patients.
- UNKNOWN – used for those interactions that are predicted, but there is insufficient evidence to hazard a guess at the outcome.

Why didn't you use another symbol?

We are indicating both severity of the interaction and also indicating the level of evidence behind an interaction. This means that there are two categories with several levels in each, and therefore it was clearer to use just the words to express these concepts.

What does it mean when you have anecdotal, theoretical or study next to an interaction?

These terms are present to indicate the evidence base on which the interactions information rests. They are defined as follows:

- STUDY – for interactions where the information is based on a formal study including those for other drugs with the same mechanism (e.g. known inducers, inhibitors, or substrates of cytochrome P450 isoenzymes or P-glycoprotein).

- ANECDOTAL – interactions based on either a single case report or a limited number of case reports.

- THEORETICAL - interactions that are predicted based on sound theoretical considerations. The information may have been derived from *in vitro* studies or based on the way other members in the same class act.

Why do you classify the level of evidence as study, but then say that the interaction is predicted to occur?

Because of an understanding of the way certain drugs affect CYP isoenzymes it is possible to make valid extrapolations across groups of enzyme inducers or inhibitors. For example, if ketoconazole affects the metabolism of a new drug by inhibiting CYP3A4 it is possible to reliably say that itraconazole will have the same effect.

Therefore if we have extrapolated study data from ketoconazole to itraconazole we use the level of evidence of 'study' but indicate that the effect is 'predicted'.

Are the levels of evidence and severity of interaction dependent on each other?

No – these are two entirely separate concepts.

Why doesn't every interaction have a severity and level of evidence?

Some of the interactions are based on the known pharmacology of a drug. For example, we know that drugs with an adverse effect resulting in lowered blood pressure are likely to have additive effects with drugs used to manage hypotension. This data doesn't come directly from investigating the interaction but is a logical result based on the known pharmacology of the drugs, and so no level of evidence has been applied. For these effects the severity can be highly variable and, quite possibly in the example given, beneficial, so no severity grading has been applied.

Where do the recommendations for action come from?

The recommendations are predominantly based on the advice provided by the manufacturers. In some instances, the advice comes from regulatory authorities or guidelines. In these circumstances, the origins of the advice are clearly stated.

Why are there no recommendations for action for some interactions?

The pharmacodynamic interactions do not usually include advice as the effect is variable, depending on factors such as dose and route of administration. It is therefore considered inadvisable to create one piece of advice when the outcome is potentially variable.

You've continued to describe some interactions by drug class. How do I know which drugs are in a class?

In the print format the members of the class are clearly displayed under the drug class heading. If an interaction applies to only some members of a drug class, the specific drugs will be included after the drug class name in the message. In digital formats, we have expanded the information and listed all interactions in drug pairs.

How are interactions handled for drugs that affect the absorption of other drugs such as colestyramine?

Yes. The manufacturers advise that the administration of colestyramine is separated from other drugs. However, because this applies across the board to the use of colestyramine we have included this information within the colestyramine monograph. We have taken this approach with a number of other drugs that are similarly said to have a universal effect, for example, other bile acid sequestrants and orlistat.

Logistics

How will I access the new interactions information?

Accessing the new interactions is simple:

- In the app, accessing the content remains the same – interactions are listed in the interactions section of the drug monograph and can be searched in the interactions checker. As before, with the BNF app, results are presented as drug pairs. Online, the search functionality also remains unchanged, and drugs are similarly presented as drug pairs.

- Accessing information in the print product will be different. The majority of the information remains in Appendix 1 providing one consistent starting point for all interactions information. Drugs are listed alphabetically as before, and if a drug is part of a drug class, all interactions for the drug will be listed under that drug class; in this case you will be directed from the drug entry to the appropriate drug class. If a drug has additional important information to be considered, such as an interaction with food, this is shown clearly beneath the drug entry; previously this information was in the drug monograph. Appendix 1 will also contain easy to use tables that bring together drugs that have pharmacodynamic effects of particular clinical significance, such as those that prolong the QT interval. Dose adjustments due to interactions will remain in the drug monograph, consistent with digital outputs.

The new interactions are much easier to use and have been designed taking user feedback into account, so we anticipate you will find navigating the content straightforward.

What are the differences between the print, app and online versions of the new BNF interactions?

While the presentation of the information differs slightly between products (mainly driven by the space constraints imposed by print) the underlying content is exactly the same.

To accommodate the interactions within the space allowed in print we have grouped interactions by drug class, and used tables to present information. In the digital formats, this information is expanded and included in drug pairs.

You can access more information at BNF.org/newbnfinteractions