

Antifungal drug interactions database and apps for iPhone and Android

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Introduction

Adverse drug reactions are frequently serious enough to result in admission to hospital. It is well recognised that adverse drug reactions (ADR) place a significant burden on the health service. Studies performed in an attempt to quantify this have shown adverse drug reactions account for 1 in 16 hospital admissions, and for 4% of hospital bed capacity.

ADRs themselves are also thought to occur in 10-20% of hospital in-patients, and one study found that over 2% of patients admitted with an adverse drug reaction died, approximately 0.15% of all patients admitted. The projected cost of ADR to the NHS in the UK is estimated at £466m (€706m, \$847m) a year. (1).

It is clear that adverse drug reactions adversely affect patients' quality of life and can also cause patients to lose confidence in the healthcare system. There is a significant impact through increase costs of patient care and the potential to lengthen hospital stays. Adverse drug reactions may also mimic disease, resulting in unnecessary investigations and delays in treatment.

Drug:drug interactions (DDIs) account for 3-5% of serious adverse reactions, which themselves are common causes of hospital admission and sometimes death. In 433 patients >60 years old taking at least 2 agents, the incidence of DDI-related ADRs was 6.5% (2, 3, 4).

DDIs are associated with increased health care use (5, 6). In the United States, the economic burden of medication-related morbidity and mortality is as high as \$177 billion (7).

Systemic azole antifungal medications have a high potential to cause DDIs with many drugs (8). Some interactions reduce the efficacy of azoles (ie rifamycins), others the efficacy of the interacting drug (ie low dose ritonavir), or lead to excess concentrations of the interacting drug (ie ciclosporin, warfarin, digoxin, benzodiazepines etc). Some interactions occur with amphotericin B and echinocandins.

Both medical professionals and patients (& carers) need support in this area because of the range and complexity of possible interactions. We have created a quick reference for guidance.

References:

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8. Roger J. M. Brüggemann^{1,4}, Jan-Willem C. Alffenaar⁵, Nicole M. A. Blijlevens^{2,4}, Eliane M. Billaud⁶, Jos G. W. Kosterink⁵, Paul E. Verweij^{3,4}, David M. Burger^{1,4}, and Louis D. Saravolatz (2009) Clinical Relevance of the Pharmacokinetic Interactions of Azole Antifungal Drugs with Other Coadministered Agents. *Clin Infect Dis*. 48 (10): 1441-1458. doi: 10.1086/598327

Methods and Data Display

Information on interactions with itraconazole, voriconazole, posaconazole, fluconazole, amphotericin B, micafungin and caspofungin has been collated from a number of sources: manufacturers' Summary of Product Characteristics, Stockley's Drug Interactions, consideration of the effects of each drug on CYP P450 isoenzymes & p-glycoprotein, clinical considerations and primary literature.

The data was recorded in a relational database table (MySQL), each row recording all information for a given drug cross referenced against all currently prescribed systemic antifungal drugs. In all we recorded 739 prescription drugs and cross referenced those with the 8 antifungal drugs listed above. 398 interactions are rated as minor, 1375 moderate and 443 severe, a total of 2216 recorded interactions.

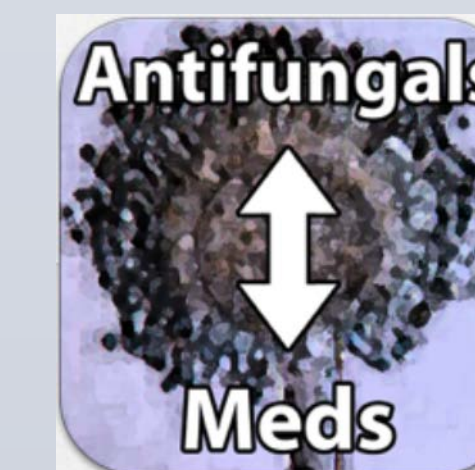
For each interacting pair of drugs the interaction is classified as of 'major' (red), 'moderate' (amber) or 'minor' (green) significance. 'Major' interactions are those that could cause significant harm, even if rare & which require avoidance, with 'minor' interactions generally increasing the risk of one or more adverse effects. Where no interaction is expected there is no entry.

For each interacting pair of drugs, the text informs the reader of the appropriate action & effects to look out for. Doctors are provided with the mechanism of the interaction, evidence of an existing interaction and action to take.

The online database is updated regularly with additional publications and constant review. The app database is updated every 6 months. It will shortly be available in a new form that will be more useful to doctors and other medical professionals, written out in a far more detailed format for professional use.

For greater access via multiple world wide web platforms we have made the database available as an online database on the Aspergillus Website (www.antifungalinteractions.org) and as smartphone APP's for both Android (via Google Play) and iPhone

(via iTunes)



Website Screenshots

The screenshot shows a web interface for checking drug interactions. At the top, there is a dropdown menu for 'Select drug' with 'bosentan' selected. Below it is a 'Check Interactions' button. A legend indicates interaction severity: Minor (green), Moderate (orange), and Severe (red). The main content area lists interactions with various antifungal drugs:

- Itraconazole:** Itraconazole may slightly increase bosentan levels. If used together, the need for dose adjustments of bosentan is not expected. As both drugs can rarely cause liver damage, your doctor will monitor liver function tests.
- Voriconazole:** Voriconazole may slightly increase bosentan levels. If used together, the need for dose adjustments of bosentan is not expected. As both drugs can rarely cause liver damage, your doctor will monitor liver function tests.
- Posaconazole:** Posaconazole may slightly increase bosentan levels. If used together, the need for dose adjustments of bosentan is not expected. As both drugs can rarely cause liver damage, your doctor will monitor liver function tests.
- Fluconazole:** The use of fluconazole with bosentan is not recommended. Fluconazole may significantly increase bosentan levels, increasing the risk of side effects. Both drugs are also associated with liver damage.
- Amphotericin B:** No interactions noted
- Ambisome:** No interactions noted
- Micafungin:** No interactions noted
- Caspofungin:** Theoretically, bosentan could decrease caspofungin levels (bosentan is an inducer of CYP2C9 and CYP3A4; levels of caspofungin have decreased during concomitant use with enzyme inducers). Your doctor may need to increase the dose of caspofungin to 70mg in those who are not clinically responding. As both drugs can affect the liver, your doctor will monitor liver function tests.

APP's Screenshots

Antifungal Interactions APP

The screenshots show the app interface on an iPhone. The first screenshot shows the 'Instructions' screen with a search box and a 'Start' button. The second screenshot shows the 'Drug List' screen with a search box and a list of drugs including abacavir/lamivudine/zidovudine, abarelix, acarbose, acetaminophen/butalbital, acetaminophen/butalbital/caffeine, acetaminophen/butalbital/caffeine/codeine, acetaminophen/propoxyphene, acetazolamide, and acetohexamide. The third screenshot shows the 'Interactions' screen for 'acarbose', displaying a key for interaction severity (Severe, Moderate, Minor) and a message: 'No Interactions were found for your selection.'

Results

Over the last 3 months (November, December 2013 and January 2014) the database has been accessed an average of 930 times per month by 360 visitors - equating to 12 users per day. APP's uptake has been low so far but this is possible due to the target audience for the first launch being patients. Those on antifungal drugs tend to be older age groups who are much less likely to own smartphones & tablets and of course this group are already regular users of the Aspergillus Website where the information can (and is) being accessed at no charge.

The database is still evolving as we add in more information and edit existing information so up until recently it has not been widely advertised. We hope to launch a more fully featured version for professionals in the next few months. Once we start making more people aware of the existence of this tool we hope to see an increase in use and increased use of the APP's as doctors start to see the usefulness of a readily available tool.

Conclusion

A DDI resource is available for antifungal drug interactions, to reduce adverse drug reactions and loss of antifungal efficacy.

Patients who experience adverse reactions have been shown to be taking ten drugs or more (3)! Under these circumstances the process of checking for interactions via the pack leaflet or Stockley's* database becomes very time consuming and complex. The professional will have a good idea of many notable interactions with common drugs but are not likely to have prescribed antifungal medication regularly, so will not be as familiar with interactions caused by those drugs. A quick, cheap, readily available resource is needed.

Our database is providing high quality information that enables patients to quickly and easily check their own medication, and will soon be able to fully support doctors as they advise their patients.

All new drugs licensed in the last 12 months will be added to update the resource in Q3 2014. Likewise anidulafungin and terbinafine will be added to the resource.

*www.medicinescomplete.com/mc/stockley/current/