OPINION ARTICLE

REVISED FDA approved drugs as potential Ebola treatments [v2; ref status: indexed, http://f1000r.es/554]

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Abstract

In the search for treatments for the Ebola Virus, multiple screens of FDA drugs have led to the identification of several with promising *in vitro* activity. These compounds were not originally developed as antivirals and some have been further tested in mouse *in vivo* models. We put forward the opinion that some of these drugs could be evaluated further and move into the clinic as they are already FDA approved and in many cases readily available. This may be important if there is a further outbreak in future and no other therapeutic is available.

This article is included in the Ebola

Open Peer Review

Referee Status: ✓ ✓

	Invited Referees 1	2
REVISED version 2 published 10 Mar 2015		✓ report
version 1 published 19 Feb 2015	✓ report	? report

1 **Raymond Lin**, Ministry of Health Singapore

2 **James Popp**, Stratoxon LLC USA

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REVISED **Amendments from Version 1**

Edits to the manuscript focus on a simple approach to using the known actives to propose additional FDA approved compounds to test. Supplemental figures have been included which show similarity searches for the molecules in Figure 1 active against the Ebola virus. A reference to our recent commentary which suggests involving the physician's perspective is included as this addresses the reviewers comment about criteria for decisions in a selection process.

See referee reports

As the Ebola outbreak continues and the costs spiral[1] we should perhaps be considering what alternative treatments are close to hand in Africa to complement the public health measures that have been used to date[2]. Two independent studies funded by the US Defense Threat Reduction Agency in 2013 identified FDA approved drugs worthy of further evaluation. This work now seems prescient although it appears to have not been followed through to any public conclusion.

In one study, the antimalarials amodiaquine and chloroquine (Figure 1) were found to be active using *in vitro* cell culture assays and an *in vivo* mouse model[3]. Both drugs are cheap, generally safe, and likely readily accessible in Africa. These compounds have also shown relatively broad activity against other viruses *in vitro* and *in vivo* in animal models (Dengue, Coronavirus OC43, SARS etc.)[4–7]. A second study suggested selective estrogen receptor modulators (SERM) clomiphene and toremifene (Figure 1) as inhibitors of Ebola virus[8]. The latter compounds are likely more accessible in the west and indicates that other FDA or EMEA approved drugs may be worth testing including those with hormonal effects that are SERMs. More recent work from 2014 in Europe identified a further 3 FDA drugs, amiodarone, dronedarone and verapamil (Figure 1) that inhibit filovirus entry at plasma levels attainable in humans[9]. The mechanism of action for most of these drugs is unknown although, using computational methods we have recently shown that the antimalarials and SERMs may share some pharmacophore features which may be important to infer a potential common target or targets[10]. To our knowledge likely well over 100 small drug-like molecules have now been identified with activity against the Ebola virus including over 50 FDA drugs derived from a reporter assay at NCATS[11–15].

As we await the development of a vaccine or biologic could we consider assessing the efficacy of the antimalarials or the other 'FDA approved drugs', as either treatments or prophylactics to prevent the Ebola virus from spreading further? While there can be no guarantee they will work (perhaps requiring adjusted dosage) they may be a last resort. It is possible there are other "non-antivirals" that are widely used in Africa that may also be effective against Ebola. Another example of where 'non-antiviral' FDA approved drugs have been found to have 'anti-viral activity' is for Hepatitis Virus B and D where the sodium taurocholate co-transporting polypeptide (NTCP) was identified as a receptor[16] and screening produced drugs such as azelastine, pioglitazone, glyburide, irbesartan and ezetimibe that inhibited the transporter and may provide potential treatments[17,18]. Of these compounds, azelastine has been shown to possess *in vitro* activity against Hepatitis Virus B to date[18].

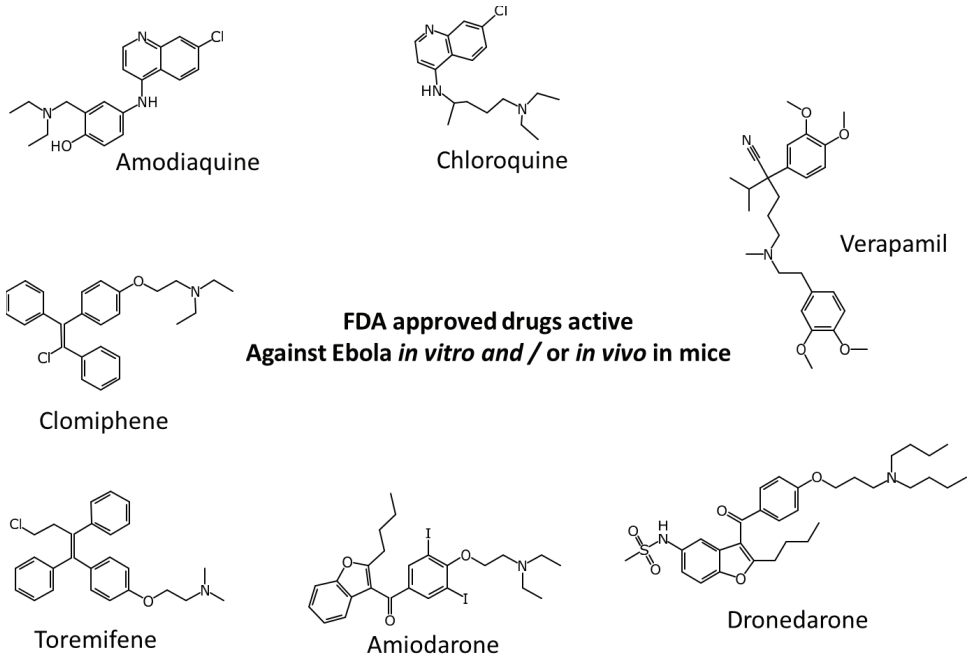

Figure 1. FDA approved drugs of most interest for repurposing as potential Ebola virus treatments.

The aforementioned screens of 'FDA approved drugs'[3,8,9] for Ebola virus activity, were far from comprehensive, covering only some of the known approved drugs currently in use. In an age where drug repurposing is in vogue[19–23] and it can be facilitated by computational methods[24–26], it would seem a valuable resource for finding compounds active against the Ebola virus. For example, the recent pharmacophores developed for Ebola[10] and virtual screens[11] could be used to computationally search larger datasets of FDA approved drugs and prioritize additional compounds for testing *in vitro*. Even using the known actives (Figure 1) to perform simple similarity searches in a set of over 1300 Approved Drugs in a mobile app (http://molmatinf.com/approveddrugs.html) could prioritize further compounds for testing (Figure S1–Figure S7). For example molecules with structural similarity to chloroquine (Figure S1) not only includes known actives like amodiaquine and hydroxychloroquine[3] but also suggests the antimalarials primaquine, halofantrine and the antihistamine chlorpheniramine. Molecules with similarity to amodiaquine include the kinase inhibitors neratinib and gefitinib while other kinase inhibitors have been suggested as having activity against Ebola virus[15], these may not be readily accessible in Africa. Other compounds retrieved by similarity include the antimicrobial pentamidine (Figure S3, Figure S4, Figure S7), the antiemetic trimethobenzamide (Figure S3– Figure S7) and the antihistamine doxylamine (Figure S5). Certainly more sophisticated and exhaustive searches than this could be tried. Deciding which molecules to use or test should also involve the physician's perspective[27]. Alternative treatments may also be found by studying those close to patients who may not have contracted the disease and are taking a drug for another chronic disease. Whether we can find a treatment for Ebola by serendipity is questionable but some of the published studies with known drugs might point us in the right direction of where to look. The opportunity to put already available drugs like those already identified[3,8,9,11–14] back on the table may be a useful tool for frontline doctors to have and is worthy of more urgent discussion and research.

Author contributions

Both authors contributed to the writing of the manuscript.

Competing interests

Neither author has competing interests.

Grant information

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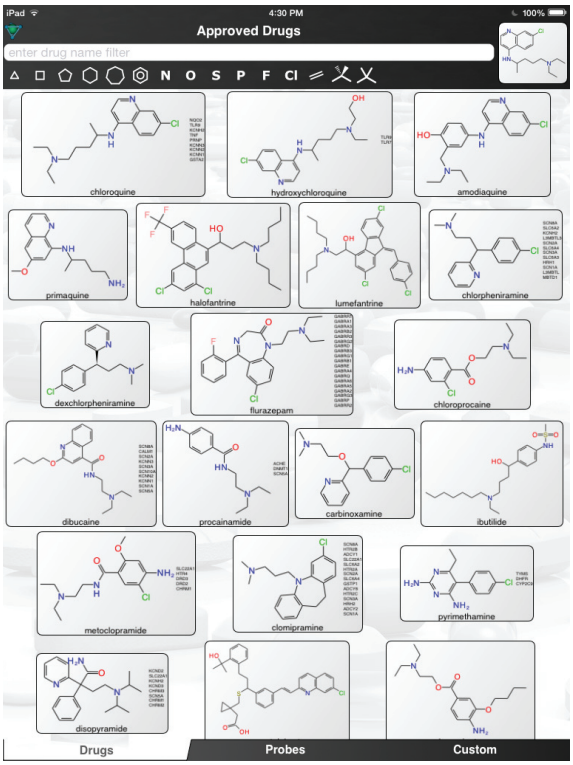
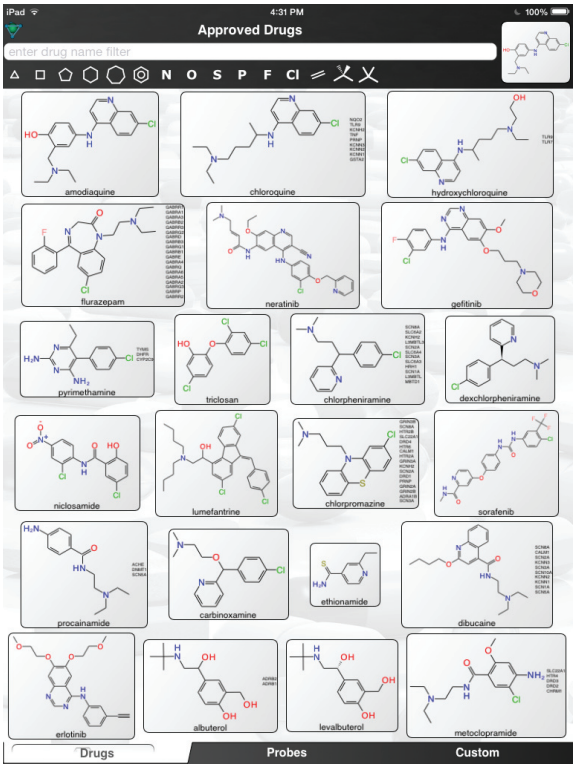
Dr. Christopher D. Southan, Dr. Joel S. Freundlich, Dr. Peter Madrid and Dr. Nadia Litterman are acknowledged for discussions on Ebola.

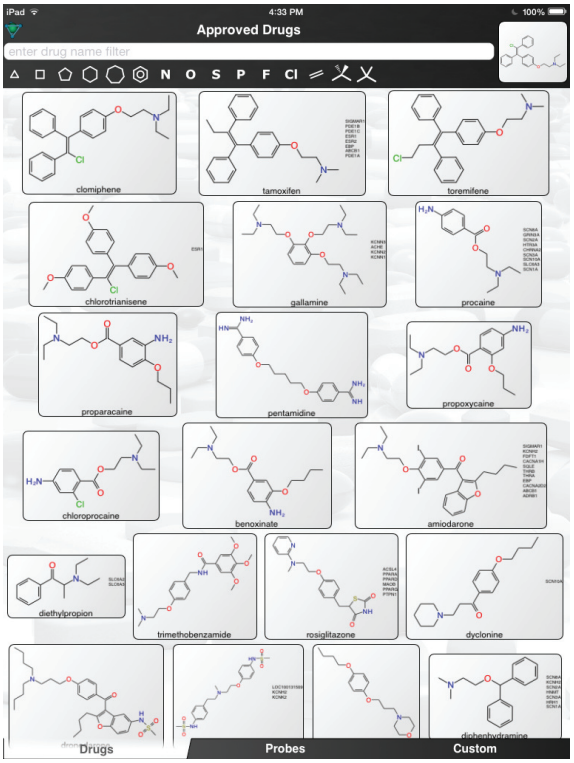
Supplementary Figures



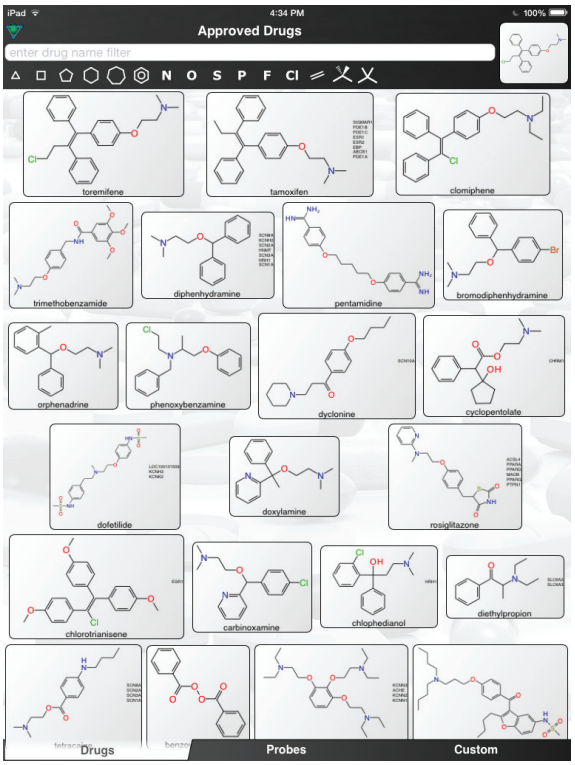
Supplemental Figure 1. Chloroquine similarity in Approved Drugs mobile app http://molmatinf.com/approveddrugs.html.



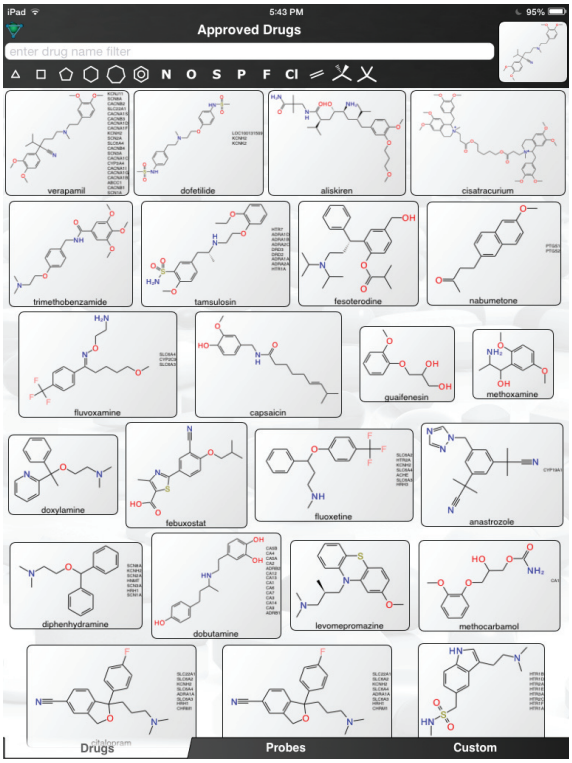
Supplemental Figure 2. Amodiaquine similarity in Approved drugs mobile app http://molmatinf.com/approveddrugs.html.



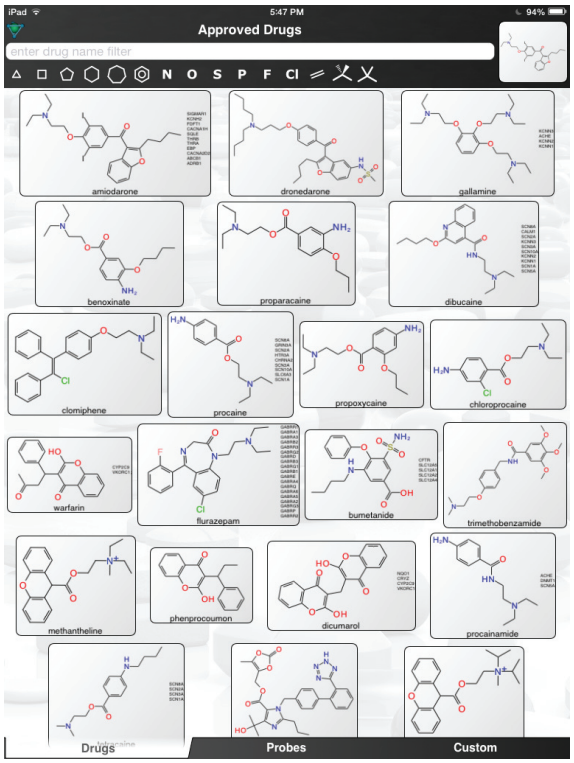
Supplemental Figure 3. Clomiphene similarity in Approved drugs mobile app http://molmatinf.com/approveddrugs.html.



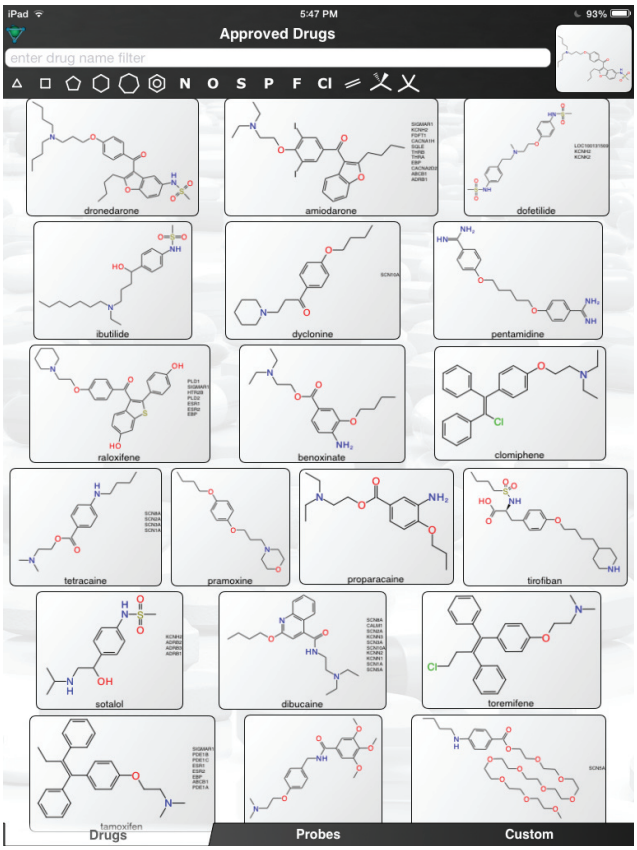
Supplemental Figure 4. Toremifene similarity in Approved drugs mobile app http://molmatinf.com/approveddrugs.html.



Supplemental Figure 5. Verapamil similarity in Approved drugs mobile app http://molmatinf.com/approveddrugs.html.



Supplemental Figure 6. Amiodarone similarity in Approved drugs mobile app http://molmatinf.com/approveddrugs.html.



Supplemental Figure 7. Dronedarone similarity in Approved drugs mobile app http://molmatinf.com/approveddrugs.html.

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Publisher Full Text

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Current Referee Status:  

Version 2

Referee Report 11 March 2015

doi:10.5256/f1000research.6664.r7908

James Popp
Stratoxon LLC, Lancaster, PA, USA

Additions included in the revised version have improved the submission.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Version 1

Referee Report 27 February 2015

doi:10.5256/f1000research.6608.r7744

James Popp
Stratoxon LLC, Lancaster, PA, USA

This Opinion Article provides an interesting and potentially important view that currently approved drugs may have activity against the Ebola virus that would allow rapid entry into clinical use due to the previous approved status. While this concept is consistent with previous scientific discussions of the potential for “repurposing” of drugs, the focus on the Ebola virus is very germane to the immediate medical crisis and the need for effective therapies related to Ebola infections. The presented opinion provides a high level overview of previously published data identifying agents with potential efficacy and the opinion appropriately expands the concept to using computational approaches to identify other drugs with potential activity. The concept of studying Ebola virus exposed individuals who did not contract the disease as an approach to identify drugs that may have a beneficial effect is very good although fraught with difficulties when such studies may be attempted under “field” conditions. This point should be expanded.

The authors are encouraged to give additional thought and provide additional opinion regarding the approach(s) that can or should be taken beyond the identification of drugs that may have potential efficacy in an Ebola outbreak. Since the opinion recommends additional screening of drugs for potential efficacy, how will (should) decisions be made to select specific agents for further evaluation or clinical

use? What criteria should be deemed essential to make decisions in a selection process? These are critical issues since limited resources (and they will always be limited) will require decisions as to which molecules will be prioritized in the selection for the next level of evaluation or use.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Author Response 02 Mar 2015

Sean Ekins, Collaborations in Chemistry, USA

Thank you for your review. In the latest version, the compounds from figure 1 with known ebola virus activity in vitro and in vivo, were used as a starting point for similarity searching >1300 FDA approved drugs in a mobile app (the same type of approach could likely be taken with other software). This would suggest several FDA approved molecules that could be readily tested and may be accessible in Africa (e.g. additional antimalarials and antimicrobials etc). While its unclear if these have been tested to date this type of approach could be taken on a larger scale. It may also point to the importance of a tertiary amine in these compounds for their mechanism.

In our most recent opinion http://f1000research.com/articles/4-58/v1 we discuss using the physician's perspective to group treatments which addresses the reviewers question of what criteria may be essential.

Competing Interests: None

Referee Report 23 February 2015

doi:10.5256/f1000research.6608.r7764

Raymond Lin
Communicable Diseases Division, National Public Health Laboratory, Ministry of Health, Singapore, Singapore

This is a different take on the approach to therapeutics for Ebola. The idea of using non-antivirals as potential therapeutics has been broached before, and it is natural to extend that proposition to Ebola. The authors provide a good summary of some candidate agents and the laboratory evidence to suggest it might be worth a try. Although the mechanistic explanation is not available, one mechanism which is common to some of them is by their effect on cell membrane transport through pores. The use of this class of drugs would also largely overcome some ethical issues which pertain to experimental drugs. Of course, in practice, the conduct of clinical trials would be more challenging than might appear. The finding of appropriate cases and controls, and the fact that mortality seems also largely determined by early access to supportive measures like re-hydration- these will complicate the ability to detect an outcome difference. On the subject of re-repurposing of drugs, we note also that some non-Ebola antivirals might be re-purposed for Ebola e.g. favipiravir, which has been approved for influenza in some countries.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Author Response 02 Mar 2015

Sean Ekins, Collaborations in Chemistry, USA

Thank you for your review and comments. We also mention favipiravir and other non-Ebola antivirals in our recent review http://f1000research.com/articles/4-38/v1.

Competing Interests: None